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PREOPERATIVE IMAGING ASSESSMENT
AND UTILITY OF THE SYSTEMIC
INFLAMMATORY INDICES IN THE
MANAGEMENT OF INVASIVE LOBULAR
CARCINOMA OF THE BREAST

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Degree of Doctor of Medicine
Institute of Life Sciences, School of Medicine

ABSTRACT

The last century has witnessed an evolution in the surgical and oncological management of breast cancer. However, the unique characteristics of lobular carcinoma continue to pose challenges in both the preoperative and adjuvant setting.

In the first part of this study, the size of lobular cancer was assessed on Digital Breast Tomosynthesis and compared with the standard imaging tool, Magnetic Resonance Imaging, using final pathology as the gold standard measurement. The correlation with sonography was calculated as a secondary analysis. The results found that lobular tumour size estimation on tomosynthesis and sonography has low to moderate correlation with final pathology. Although, there is some agreement with tumour sizes less than 2cm, the need for preoperative MRI remains. The introduction of contrast-enhanced spectral mammography may reduce the need for magnetic resonance imaging in the preoperative assessment of lobular breast cancer. Further investigation will be considered.

The second analysis evaluated the potential of systemic peripheral blood ratios as prognostic indicators in the adjuvant setting of node negative early breast cancer, comparing two internationally validated tools, the Nottingham Prognostic Index and Oncotype DX® Recurrence Score, to assess whether the blood ratios may reduce the need for genomic testing in selected cases. The recurrence scores of 495 node negative patients with early breast cancer were compared with the Nottingham Prognostic Index and four systemic inflammatory indices calculated from the preoperative peripheral blood count. Statistical tests of correlation found that there was poor to no correlation with the Oncotype DX® Recurrence Score, the Nottingham Prognostic Index and the systemic inflammatory indices investigated, for both subtypes.

The results of this study highlight the need for further work in this field. Lobular cancer has distinct morphomolecular and histomolecular properties that require studies specifically designed to address this.

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

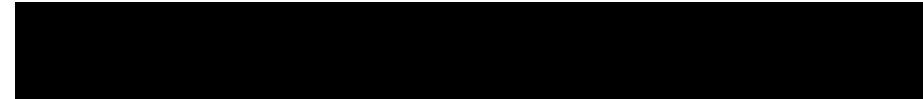
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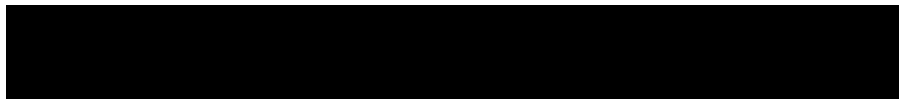
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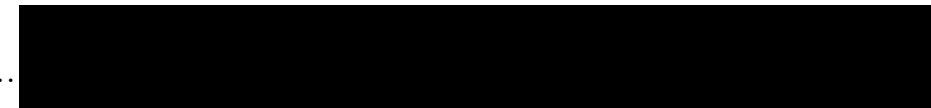
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The university's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.

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ABBREVIATIONS

| | |
|---------|--------------------------------------------------------------|
| AD | Architectural Distortion |
| BCI | Breast cancer Index |
| BI-RADS | Breast Imaging and Reporting Data System |
| BRCA | Breast Cancer Gene (1 or 2) |
| BTW | Breast Test Wales |
| CAD | Computer Aided Detection |
| CANISC | Cancer Network Information System Cymru |
| CC | Craniocaudal |
| CDR | Cancer Detection Rate |
| cHRT | Combined Hormone Replacement Therapy |
| CI | Confidence Intervals |
| C-view | Synthetic 2D mammography images (s2D) |
| DBT | Digital Breast Tomosynthesis |
| DCE-MRI | Dynamic Contrast-Enhanced Magnetic Resonance Imaging |
| DFS | Disease free survival |
| DM | Digital Mammography (also known as FFDM) |
| DCIS | Ductal Carcinoma in situ |
| EPclin | EndoPredict® assay combined with tumour size and node status |
| ER | Oestrogen Receptor |
| FBC | Full Blood Count |
| FDA | Food and Drug Administration (USA) |
| FFDM | Full Field Digital Mammography (also referred to as DM) |
| GGI | Genomic Grade Index |
| GPS | Glasgow Prognostic Score (mGPS – modified) |
| H&E | Haematoxylin and Eosin Staining |

| | |
|---------|----------------------------------------------------|
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HDUHB | Hywel Dda University Health Board |
| ICC | Intraclass Correlation Coefficient |
| IDC | Invasive Ductal Cancer |
| ILC | Invasive Lobular Cancer |
| IQR | Interquartile Range |
| LBCCA | The Lobular Breast Cancer Care Alliance |
| LCIS | Lobular Carcinoma in situ |
| LVI | Lymphovascular Invasion |
| MDT | Multidisciplinary Team |
| MLO | Medial Lateral Oblique |
| MLR | Monocyte Lymphocyte Ratio |
| MRI | Magnetic Resonance Imaging (see DCE-MRI) |
| NACT | Neoadjuvant Chemotherapy |
| NCDB | National Cancer Database |
| NET | Neoadjuvant Endocrine Therapy |
| NICE | National Institute for Health and Care Excellence |
| NHS BSP | National Health Service Breast Screening Programme |
| NLR | Neutrophil/Lymphocyte Ratio |
| NOS | Not otherwise specified (referring to IDC) |
| NST | No special type (referring to IDC) |
| NPI | Nottingham Prognostic Index |
| ODX | Oncotype DX Test |
| OS | Overall Survival |
| PACS | Picture Archiving and Communication System |
| PICO | Population, Intervention, Comparison, Outcome |
| PLR | Platelet Lymphocyte Ratio |

| | |
|------|------------------------------------------------------------------|
| PPH | Prince Philip Hospital |
| PR | Progesterone Receptor |
| RCT | Randomised Controlled Trial |
| RR | Recall Rate (referring to mammogram recalls following screening) |
| RS | Recurrence Score |
| SD | Standard Deviation |
| s2D | Synthetic 2D imaging (C-view in Hologic) |
| SEER | Surveillance, Epidemiology and End-Results data |
| SII | Systemic Inflammatory Indices |
| USS | Ultrasound Scan (also known as sonography) |
| VAB | Vacuum Assisted Biopsy |
| WCP | Welsh Clinical Portal |
| WHO | World Health Organisation |

CHAPTER 1: GENERAL INTRODUCTION

1.1 BREAST CANCER

1.1.1 Epidemiology

The number of newly diagnosed cancer cases in the western world continues to rise, with breast cancer as the most common malignancy in women, accounting for 25% of all cancers (Sung, et al., 2021). It is one of the leading causes of cancer deaths in females worldwide (Althuis, et al., 2005; Sung, et al., 2021). The United Kingdom (UK), along with many developed countries, has seen an increase in the incidence of breast cancer; with approximately 55,000 newly diagnosed cases recorded in England and Wales in 2020, comprising nearly a third of cancer registrations in women (Office for National Statistics., 2017; Smittenaar et al., 2016. Welsh Cancer Intelligence and Surveillance Unit., 2022). The highest fold increase had been noted in the proportion of cancers with a lobular component (Li et al., 2003); although, the latest statistics suggest that this difference has become less evident (Dossus & Benusiglio, 2015). In general, the incidence of breast cancer plateaued in early 2000, a possible effect of a reduction in the use of hormone replacement therapy at that time, coupled with effective screening programmes. However, since 2007, the incidence of hormone receptor positive breast cancer has risen steadily. This has been attributed in part to obesity, diet, and perversely breast screening, which preferentially detects slow growing tumours (Sung, et al., 2021). Interestingly, the use of HRT has been steadily rising again as public awareness and social campaigns have promoted the benefit of oestrogen therapy for menopausal symptoms (Alsugeir et al., 2022). This may result in an increase in the incidence of lobular breast cancers in the UK in the future.

In the United Kingdom, the incidence of breast cancer increases with age. A sharp increase is seen in the 4th to 6th decade of life (Figure 1.1), which partly explains the screening age currently deployed in the UK.

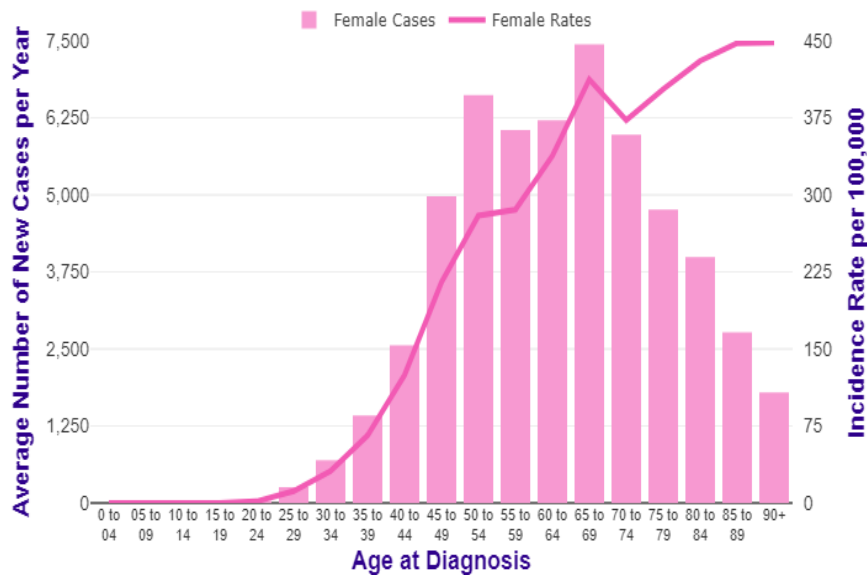


Figure 1.1 Incidence of breast cancer with age. UK Data, 2016 - 2018. Cancer Research UK

The age group of women in the UK invited for triennial mammography in the Breast Screening Programme is currently 50 to 70 years old. There has been considerable debate surrounding the benefit of screening women from 40, with one independent review concluding that harm outweighed benefit (Hackshaw, 2012; Marmot et al., 2013). A study in 2020 readdressed the issue of entry age at first screening with findings indicating that mammography from 40 years of age could potentially reduce mortality (Duffy et al., 2020; Helvie & Bevers., 2018). However, in the current financial climate the implications of introducing breast screening at a younger age are such that this may be reconsidered. At the other end of the scale, a recently published retrospective study reviewing mortality data from the UK NHS Breast screening programme (NHS BSP) between 2009 and 2013, concluded that when screening women over the age of 70, the risk of harm may outweigh benefit (Savaridas et al., 2022). Mammography in screening is discussed in more detail in Section 1.4.

1.1.2 Anatomy and Physiology of the Adult Female Breast

The breast is essentially a modified sweat gland composed of skin, subcutaneous tissue and breast tissue, with the latter comprised of stromal and epithelial elements (Figure 1.2). In the adult female, there are between 15 and 20 breast lobes which are further divided into lobules. These lobules are glandular structures that contain alveolar glands

which are responsible for milk production during lactation. The lobules are drained by lactiferous ducts which open via a sinus into the nipple.

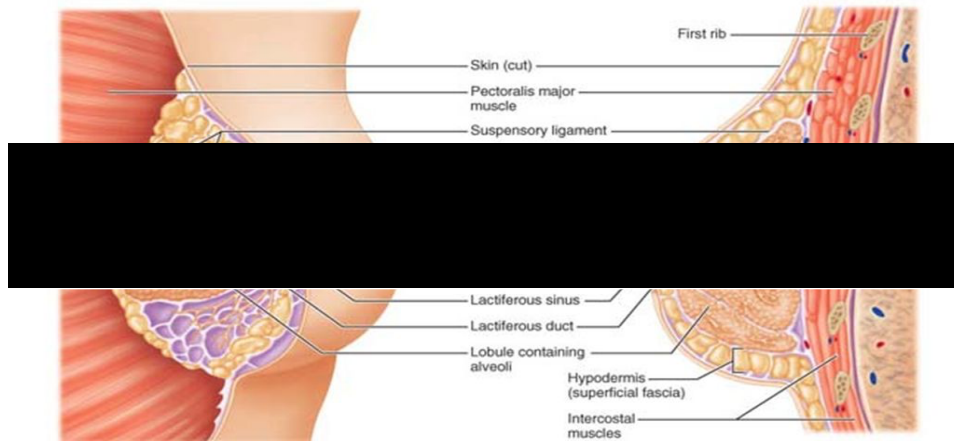


Figure 1.2 Cross-section of the anatomy of the adult female breast

Note: Illustration. Benjamin Cummings. Copyright © 2001. An imprint of Addison Wesley Longman Inc.

Anatomically, the breast is situated between the second rib superiorly and the sixth rib inferiorly. Breast tissue can also be found within the axilla, at the midline adjacent to the sternum, and as far lateral as the midaxillary line. For this reason, imaging of the breast by mammography is usually performed in two views to obtain the maximum amount of tissue within the imaging field: mediolateral oblique (MLO) allowing for adequate imaging of the lateral aspect of the breast and the axilla, and the craniocaudal (CC) view for maximum compression (Figure 1.3). Compression of the breast is important in mammography as it enhances image quality by reducing breast thickness and overlapping of tissue, thereby improving visualisation of abnormalities. Compression reduces motion artifact and blurring of the image, resulting in a more uniform image of the breast. Another important consideration is that compression has been shown to reduce radiation dose (Loveland et al., 2022). Mammographic technique is discussed in more detail in Section 1.4.

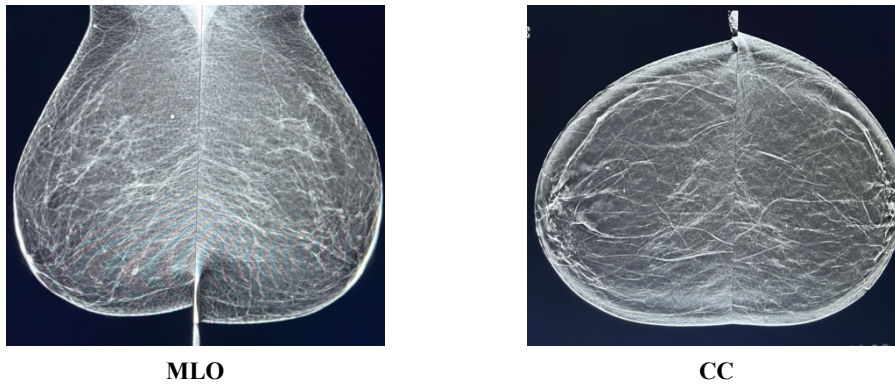


Figure 1.3 Standard 2 view mammogram of both breasts.

Note: Mediolateral Oblique (MLO) and Craniocaudal (CC). Images courtesy of Hywel Dda University Health Board.

The main function of the breast is lactation. Prior to puberty, the breast consists of ducts with blind-ended acini that converge toward the nipple. Thelarche, the commencement of breast development, is mostly driven by the rise in oestrogen associated with puberty which stimulates the growth of the duct system and maturation of the nipple (Lin et al., 2023). The elevated levels of progesterone and oestrogen result in duct acini maturation and proliferation (Lin et al., 2023). At the other end of the reproductive cycle, the levels of oestrogen and progesterone reduce toward the menopause, resulting in lobular involution and a consequent reduction in the density of the breast as the amount of fibroglandular tissue in the breast decreases (Milanese et al., 2006; Radisky et al., 2016). This change is associated with a relative increase in the fat composition of the breast, termed fatty involution (see 1.1.2.1). Interestingly, studies have shown that the extent of involution is related to breast cancer risk, as discussed below (Boyd et al., 2007; Bodewes et al., 2022; Ginsburg et al., 2008).

1.1.2.1 Breast Density

Breast density refers to the amount of fibroglandular tissue relative to fat in the adult female breast. The constitution of breast tissue is dependent on several factors including age, hormonal status, body habitus, genetics (Boyd et al., 2009), and in addition, to exogenous oestrogen (Burton et al., 2017; Ghosh et al., 2012). The supporting fibrous network within the breast connecting the superficial and deep fascial layers are known as Coopers ligaments. These ligaments, coupled with the connective and glandular tissue, contribute to the density of breast tissue. With age,

the composition of breast tissue changes as ducts and lobules reduce in number, and stromal and adipose tissue predominates (Burton et al., 2017; Henson & Nsouli, 2015; Lin et al., 2023). This fatty involution of the breast is variable between individuals, with some patients retaining dense breast tissue into their 8th decade (Ji et al., 2021). As density of breast tissue is inversely related to the sensitivity of imaging by mammography, it follows that the positive predictive value of breast imaging increases in fatty involuted breasts (Figure 1.4) (Lokate et al., 2013; Mann et al., 2022).

The Breast Imaging Reporting and Data System (BI-RADS) is a validated reporting and classification system for mammography, sonography, and magnetic resonance imaging (MRI), designed by the American College of Radiology. The latest edition is the 5th BI-RADS (Sickles et al., 2013). It is peer reviewed and enables standardisation of reporting and quality assurance. The BI-RADS density scores breast composition into 1 of 4 categories; mostly fatty (A), fatty with scattered islands of fibroglandular tissue (B), heterogeneously dense (C) and extremely dense (D) (Figure 1.4).

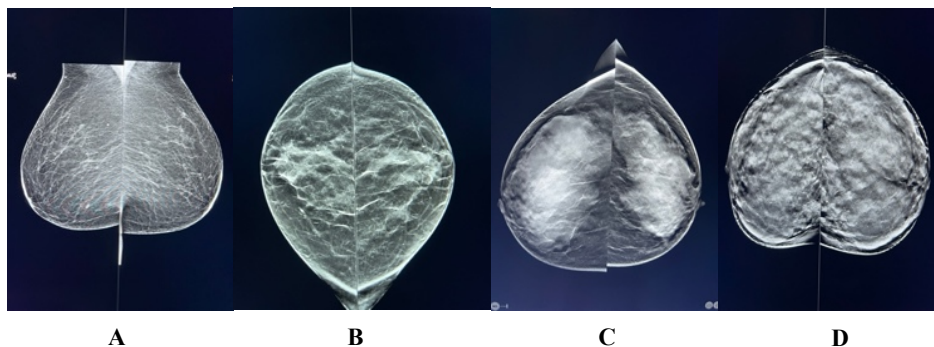


Figure 1.4 BI-RADS Breast density categories on tomosynthesis

Note: A Fatty; B Scattered Fibroglandular Islands; C Heterogeneously Dense; D Dense. Tomosynthesis images from Hywel Dda Health Board Library.

With the introduction of digital mammography and tomosynthesis, the assessment of breast density has become more reproducible. Algorithms computing breast density have been assessed in studies comparing results with BI-RADS (5th Edition). The findings demonstrate good agreement especially when breast density is divided into two categories, fatty and dense (Figure 1.4 above). Studies evaluating the software system Quantra, which is used with the Hologic tomosynthesis system, suggest that with two category density grouping, the agreement with BI-RADS for fatty and dense breast tissue, is 97.1% and 83.1% respectively (Ekpo et al., 2016).

Breast density is an independent risk factor for breast cancer, with studies suggesting that there is a one to six-fold increase with increasing breast density (Bodewes et al., 2022; Boyd et al., 2007; Engmann et al., 2017; Ginsburg et al., 2008; Pettersson et al., 2014; Vacek & Geller, 2004). The systematic review and meta-analysis by Bodewes and colleagues (2022), found a two-fold increase in breast cancer risk for density category D. These issues are compounded as breast density is inversely related to mammographic sensitivity to breast cancer detection (Chiu et al., 2010). Studies assessing the sensitivity of digital mammography in dense breast tissue found detection rates between 62% and 68% in all breast tumour subtypes (Carney et al., 2003; Freer., 2015), with sensitivities for detection of ILC in extremely dense breast tissue reported to be as low as 13% in some studies (Weaver et al., 2020). A large prospective multicentre study in the USA published in 2015, found the sensitivity for digital mammography in fatty breasts was 81-93%, in Category B 84-90%, in Category C 69-81%, and in extremely dense breast tissue (D) 57-71% (Kerlikowske et al., 2015). A systematic review and meta-analysis evaluating cancer detection rates in dense breast tissue, comparing digital breast tomosynthesis (DBT) and digital mammography from 11 screening studies and 5 diagnostic studies, (Phi et al., 2018) concluded that although tomosynthesis has a higher sensitivity when compared with digital mammography, there are still recognised limitations in very dense breast tissue (Phi et al., 2018; Rafferty et al., 2016).

This is evident in practice, as it is well documented that mammographic recall rates and missed cancer rates are higher in density category C and D when compared with patients with fatty breast tissue (Boyd et al., 2007; Mandelson et al., 2000). Additionally, mammographic tumour measurement is affected by breast density, with significant size discrepancies between imaging and histology found in many of the older studies that used digital mammography (Fasching et al., 2006). More recent studies suggest that although size assessment of tumours in dense breast tissue has been improved by tomosynthesis (Chudgar et al., 2017), the evaluation of lobular cancers still requires additional evaluation with MRI imaging (Chamming's et al., 2017; Marinovich et al., 2018).

1.1.3 Lymphatic Drainage of the Breast

Preoperative assessment and staging of the axilla is as important today as it was in the day of the Halstedian mastectomy. The presence of axillary nodal disease determines preoperative investigation and management. Studies on cadavers confirm that almost 90% of the lymphatic drainage of the breast is to the ipsilateral axillary nodes, with 10% to the internal mammary chain (Suami et al., 2008). Assessment of the axilla in patients with newly diagnosed breast cancer is important in the preoperative setting. Breast sonography is performed, and if the lymph nodes appear abnormal, they are biopsied under ultrasound guidance. Tumour spread to the axillary nodes is an important prognostic indicator and is recognised in one of the three components of the TNM Staging (see Section 1.3.4). However, the management of the axilla has been evolving since the days of axillary nodal clearance. The introduction of the method for identification and biopsy of the sentinel node opened the path to less extensive axillary surgery, with studies finding similar survival outcomes for patients with node-negative or low level axillary involvement treated with sentinel node biopsy, with or without radiotherapy (Lyman et al., 2017).

Interestingly, studies have found that sonographic preoperative assessment of the axilla in lobular patients may not always identify abnormal nodes (Chung et al., 2022; Fernández et al., 2011), and, in addition, pathological assessment of the axillary nodes in lobular breast cancer can also be challenging, which is thought to be partly due to the effect of E-cadherin (Fernández et al., 2011; Sledge et al., 2016). These difficulties are compounded when investigating patients with lobular cancer, as some studies have also noted an increased risk of nodal positivity in this subgroup (Danzinger et al., 2023; Fernández et al., 2011; Oesterreich et al., 2022). However, a landmark study, the Z0011 trial, evaluating the need for further axillary surgery if the sentinel node is found to be involved, concluded that although lobular histology was associated with a higher rate of non-sentinel node involvement, this did not result in poorer outcomes for patients with ILC compared with IDC (Mamtani et al., 2019). The authors found that further axillary surgery was not a prerequisite in lobular tumours with limited sentinel node involvement. The length of follow-up of the trial was two years. This may be too short a period to predict recurrence potential, as ILC often recurs years after diagnosis. Additionally, important prognostic information obtained from axillary clearance, that

is the number of axillary nodes involved with disease, could be missed, potentially resulting in understaging and undertreatment of these patients (Narbe et al., 2023). Currently in the UK, management of a positive sentinel node in all breast cancer types is being reviewed in response to publication of the results of the AMAROS trial (Bartels et al., 2023), and a working group in the UK is undertaking review into the management of the axilla, the results of which are eagerly awaited (Weber et al., 2023).

1.1.4 Histological Types of Breast Cancer

The term ‘breast cancer’ encompasses a heterogenous group of tumours with a variety of histological and biological features which have different presentations and clinical outcomes. However, most breast tumours, regardless of their subtype, arise within the terminal ductal lobular units (TDLU) of the breast (Tabár et al., 2022). The TDLU is the basic functional unit of the breast ranging between 1 and 4mm in size (Tabár et al., 2022). It is comprised of 3 to 50 acinar cells grouped together in a lobule along with associated ducts. Interlobular and intralobular stromal structures are composed of connective tissue, containing collagen fibres, adipose tissue, blood, and lymphatic vessels which provide structural support for the TDLU (Tabár et al., 2022) (Figure 1.5).

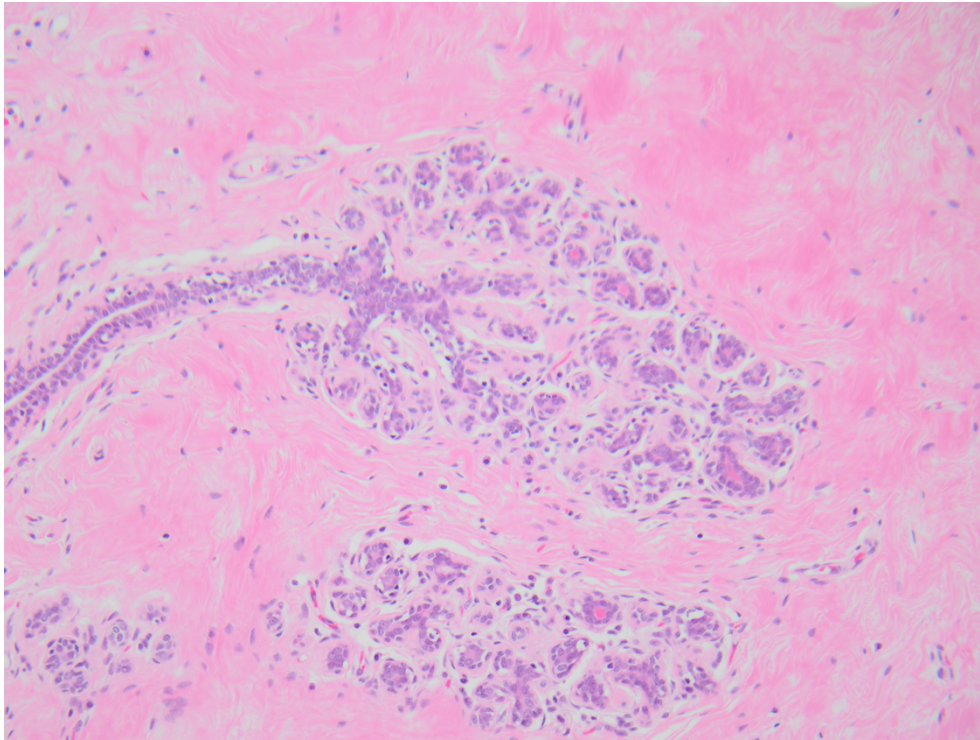


Figure 1.5 Terminal Ductal Lobular Unit of the female breast

Note: Pathology Slide illustrating a low power (10x) thin histological image of a Terminal Ductal Lobular Unit (TDLU) stained with H&E. Kindly donated by Dr Tim Murigu Consultant Histopathologist Morrision Hospital ABMU, Swansea.

The ductolobular system is lined by a dual layer of epithelial cells on a basement membrane surrounded by stroma. These cells express hormone receptors, such as oestrogen receptor (*ER*) and progesterone receptor (*PR*), that respond to the hormonal stimuli during pregnancy and the menstrual cycle (Stingl., 2011). Oestrogen receptor signalling is also integral in carcinogenesis. Between 70 and 80% of all breast tumours overexpress this receptor. *ER* and *PR* are independent prognostic and predictive markers in breast cancer, as they predict response to targeted treatment. These receptors are discussed in more detail in Section 1.2.2.

The histological classification of breast cancer is based on guidelines from The World Health Organisation (WHO). The most common type of breast cancer is Invasive ductal cancer (IDC), which is also annotated, and internationally recognised as Ductal No Special Type (IDC/NST), or Ductal Not Otherwise Specified (IDC/NOS). IDC is a group of malignancies that cannot be categorised into the specific histological classifications, as defined by the WHO. The latest edition, published in 2019, lists the breast cancers that comprise the other breast tumour types (Tan et al., 2020). As the

study is assessing the most common special type of breast cancer, ILC, the histology of this and IDC will be discussed, as there are distinct clinicopathological features that are unique to the lobular subtype.

1.1.4.1 Invasive Ductal Carcinoma of the Breast

The most prevalent histologic type is IDC comprising 70%-80% of all breast tumours, with lobular cancers accounting for 5-15% (Arpino et al., 2004; Christgen et al., 2016; Dossus & Benusiglio, 2015; Li et al., 2003; Wilson et al., 2020). As previously mentioned, the diagnosis of IDC is one of exclusion, as the diagnosis is made when the pathological features are not consistent with the special types of breast cancer, as defined in the WHO classification (Tan et al., 2020). The pathological findings of IDC can be heterogeneous. The WHO subcategorises ductal tumours with mixed histological features, into those with mucinous features or medullary features, and the mixed ductal-lobular carcinoma. This latter classification has had renewed interest, as studies appear to suggest that these types have outcomes that are more aligned with lobular cancers, although to date, they have been grouped with the ductal cohorts (Arps et al., 2013; Nasrazadani et al., 2023; Rakha et al., 2007). This is discussed further in Section 1.2.1.

1.1.4.2 Invasive Lobular Carcinoma of the Breast

There are clinicopathological differences between IDC and ILC, with some specific and unique features affecting the detection and assessment of the latter. The tumour growth pattern, which is more diffusely infiltrative in ILC, results in less of a desmoplastic reaction than that caused by IDC (Figure 1.6) This partly explains why the tumour can be more difficult to detect mammographically when compared with other breast cancer subtypes and is more often seen as an architectural distortion than ductal cancers (Bane et al., 2005; Chamming's et al., 2017; Grubstein et al., 2016). This is especially relevant in patients with dense breast tissue where mammographic sensitivity to cancer detection in all subtypes can be as low as 34-75% (Berg et al., 2004; Porter et al., 2014; Wanders et al., 2017). In addition, ILC is less frequently associated with microcalcifications than ductal tumours, which can also make detection more difficult (Arpino et al., 2004; Johnson et al., 2015), (Section 1.5.1.4).

1.2 HISTOPATHOLOGICAL FEATURES OF ILC

In 1941, Foote and Stewart described the single-file growth pattern of a breast cancer that was termed lobular carcinoma. Subsequently in the 1990's, research identified the loss of a transmembrane protein in this subtype, E-cadherin, which is now recognised as a defining feature of lobular tumours (Gamallo et al., 1993; Moll et al., 1993). Most ILC are distinguished by this loss of E-cadherin, an adhesion molecule which is integral to several intercellular functions (Rakha et al., 2010; Ciriello et al., 2015). In ILC tumour growth, this lack of cell cohesion results in an insidious growth pattern through the breast tissue, causing less of a desmoplastic reaction compared with other subtypes of breast cancer (Moll et al., 1993) (Figure 1.6). The unique growth pattern of this special breast tumour subtype means that lobular breast cancer is often more difficult to detect both on clinical examination and imaging, such that, at presentation the tumours can be larger than the more common breast cancer, IDC (Arpino et al., 2004; Yang et al., 2017), and are more often missed on standard imaging (Gilliland et al., 2000; Porter et al., 1999). These features are explored in greater detail in Section 1.5.

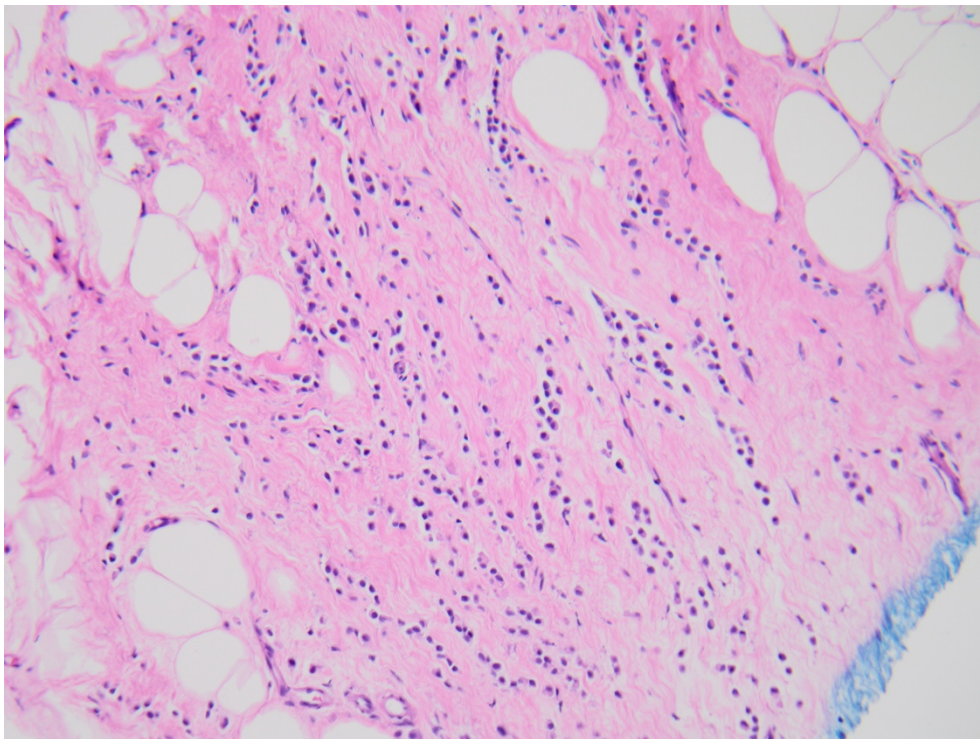


Figure 1.6 Single-file growth pattern of Invasive Lobular Breast Cancer

Note: High power (x10) H&E stained slide kindly donated by Dr Tim Murigu Consultant Histopathologist, Morrision Hospital, Swansea.

1.2.1 Morphological Characteristics Invasive Lobular Carcinoma

Lobular breast cancer is the most common special type of breast cancer. Despite significant advances in knowledge regarding the unique biology of ILC, with studies into lobular breast cancer modelling incorporating the heterogeneity of lobular breast cancer into research (Sflomos et al., 2021), there is still a paucity of data exclusively evaluating this tumour in the literature. The characteristic growth pattern of ILC is described as single cell file infiltration through the breast stroma, with little disturbance of the surrounding architecture, as described and seen above (Figure 1.6). There are morphological variants of ILC which exhibit variation from the classic form in cytology and/or architecture and include subtypes, such as the alveolar type, solid type, tubule-lobular, pleomorphic and mixed ductal-lobular carcinoma (Li et al., 2003). The pleomorphic ILC variant has a similar growth pattern to the classic type of lobular cancer; although, it exhibits marked cellular atypia, which is often associated with an increase in mitotic rate (McCart Reed et al., 2015) This is seen in Figure 1.7.

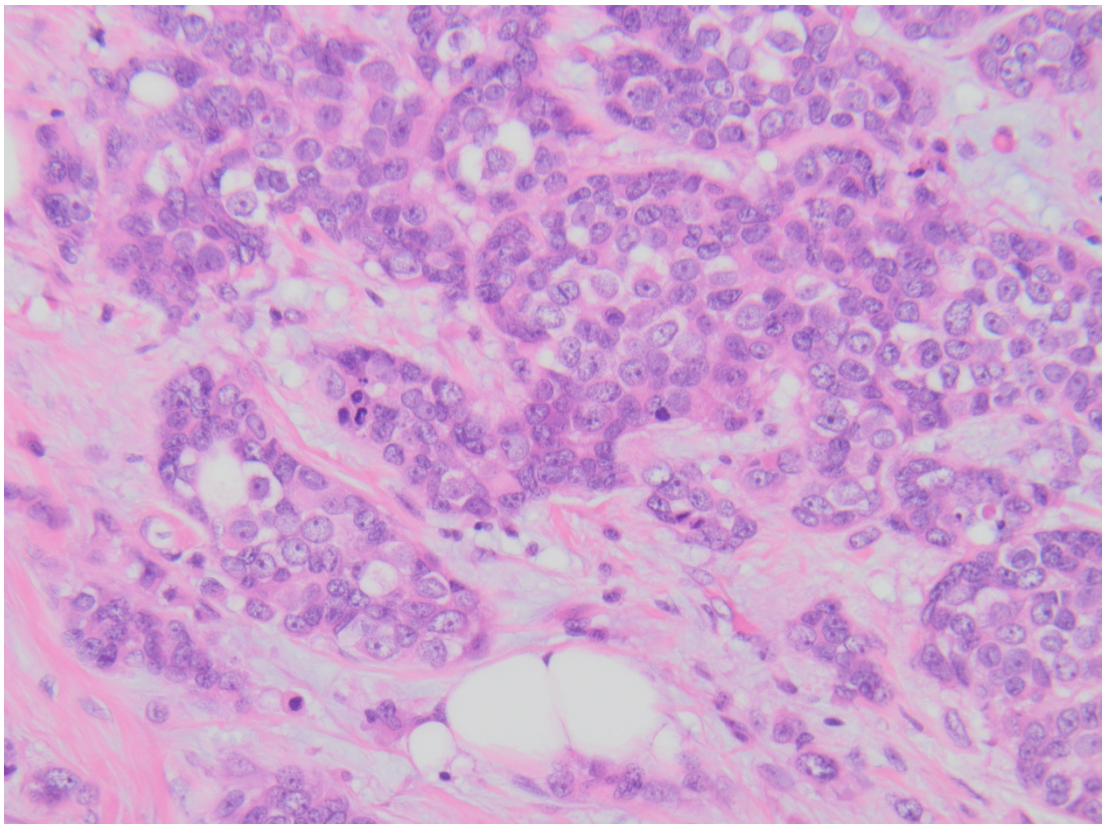


Figure 1.7 Histopathology Pleomorphic Invasive Lobular Breast Cancer

Note: H&E stained. High power (x10) view of a pleomorphic variant of ILC demonstrating irregular nuclei, kindly donated by Dr Tim Murigu Consultant Histopathologist Morrision Hospital, Swansea.

The mixed ductal lobular variant is classified according to the 2019 World Health Organisation (WHO), where at least 10% of the tumour is characterised as IDC NST (Tan et al., 2020). A recent large retrospective analysis of the clinicopathological features and outcomes of 12,979 IDC, 1569 ILC and 803 patients with mixed IDC/ILC (mIDC/ILC) was performed alongside a meta-analysis of 23 similar studies. The study concluded that the mixed pathology type was most aligned with lobular characteristics and outcomes (Nasrazadani et al., 2023), reaffirming the results of earlier studies into mIDC/ILC (Arps et al., 2013; Rakha et al., 2007). However, there is a general lack of research assessing imaging pathology concordance in this subgroup of breast cancer exists.

The importance of histological grading in tumour classification is well established, although, the relevance of lobular breast cancer grading has been a topic of discussion as the pathological features that assess grade, such as tubule formation, nuclear pleomorphism and atypia, and mitotic count, are fairly uniform in classical ILC (Oesterreich et al., 2022). In general, lobular cancers have low mitotic counts, low nuclear pleomorphism, with little, if any, tubule formation (McCart Reed et al., 2015; Rakha et al., 2008). Consequently, most lobular cancers are graded as Grade 1 or 2, with approximately only 10% classified as Grade 3 (Engstrøm et al., 2015; Iorfida et al., 2012; Rakha et al., 2008). Interestingly however, studies evaluating the prognostic value of grading systems have concluded that histological grade in ILC is a strong predictor of survival and should be included in pathology reports (Pramod et al., 2021; Rakha et al., 2008; Rakha & Ellis, 2010). Indeed, research has shown that the majority of classic ILC are Grade 2 tumours, with some cases Grade 1. The pleomorphic subtype accounts for approximately 15% of all lobular neoplasms. These tumours are often Grade 3 and are associated with a worse prognosis (Iorfida et al., 2012; Orvieto et al., 2008). Grading systems are discussed in more detail in Section 1.8 (Prognostic testing in ILC).

1.2.2 Immunophenotypic Profile Invasive Lobular Carcinoma

The improvement in breast cancer outcomes is in part a consequence of seminal research into molecular profiling of breast cancer. The identification of hormonal

receptor expression, and the research into targeted therapies, has been one of the important developments in breast medicine, as knowledge of the receptor status facilitates treatment stratification and prognostication. Tumour expression of oestrogen and progesterone is assessed by immunohistochemistry (IHC) using an internationally recognised test, the Allred system (Allred et al., 2009). The Allred scale is calculated on the proportion and intensity of IHC staining in the nucleus. Hormone receptor results are expressed as a level out of 8: 0-2 are considered negative for *ER*, 3/8 to 8/8 positive, with 8/8 being strongly positive. Although this scoring system is clinically validated, it is well recognised that there can be discrepancies in laboratory reporting, especially with lower levels of *ER* positivity (Allison et al., 2020; Allred et al., 2009; Hammond et al., 2010). This variability is often cited as a potential confounding factor in studies, such that central laboratory pathology review in studies should be considered to avoid errors in reporting (Hammond et al., 2010). The *ER* and *PR* are important predictive and prognostic indicators for response to adjuvant endocrine therapy and chemotherapy, such that accurate reporting is essential for treatment planning (Allred et al., 2009; Hammond et al., 2010).

Most breast cancers overexpress *ER* and *PR* (Lim et al., 2012), with studies confirming that 90% and 70% of lobular breast cancers express *ER* and *PR*, respectively (Arpino et al., 2004; Orvieto et al., 2008; Rakha et al., 2008). Several receptors, such as the androgen receptor and *ERβ*, are also frequently overexpressed in ILC (Rakha & Ellis, 2009). The biomarker Human epidermal growth factor receptor (*HER2*) is less frequently overexpressed in ILC when compared with IDC, although, it is more commonly found in the pleomorphic and solid types of ILC (Arpino et al., 2004; Christgen et al., 2019; Rakha et al., 2008). The presence of overexpression of these receptors is important for planning management and adjuvant treatment decisions. The high expression of *ER*, *PR*, and low levels of *HER2* positivity, coupled with low mitotic rate in lobular cancers, may contribute to the relatively low chemosensitivity seen in many patients with this breast cancer subset (Arpino et al., 2004; Oesterreich et al., 2022).

Another common feature of ILC is the loss of E-cadherin, a molecule that mediates cell adhesion, with approximately 90% of ILCs lacking expression (Pramod et al., 2021) (Section 1.2). This lack of E-cadherin is a consequence of alterations to the

CDHI gene (Christgen & Derkson, 2015; Ping et al., 2016). Other mutations in ILC have been identified by the Cancer Genome Atlas Study (Ciriello et al., 2015; MA & Ellis, 2013; Sledge et al., 2016) and a number of these are currently under study for development of new targeted therapies, such as PDL1 immunotherapy treatment (Sledge et al, 2016; van Baelen et al., 2022).

1.2.3 Preinvasive lesions associated with Invasive Lobular Carcinoma

There are two main preinvasive pathologies that can be associated with ILC, both of which can appear as microcalcification on standard imaging. These are Ductal Carcinoma in situ (DCIS) and Lobular Carcinoma in situ (LCIS), both of which can be associated with the presence of extensive microcalcification, which has been shown to increase discordance between radiological and histological tumour measurements (Nonnemacher et al., 2023; Nyante et al., 2017).

1.2.3.1 Ductal Carcinoma In-Situ

Ductal Carcinoma in situ (DCIS) is a heterogenous group of pathologies that can be associated with lobular breast cancers (Abdel- Fatah et al., 2007). In DCIS, tumour cells expand the duct within the TDLU without invading the basement membrane (Figure 1.8). Image detected calcifications are present in most cases. Studies suggest that MRI estimates the extent of DCIS disease more accurately than mammography and sonography (Bartram et al., 2021).

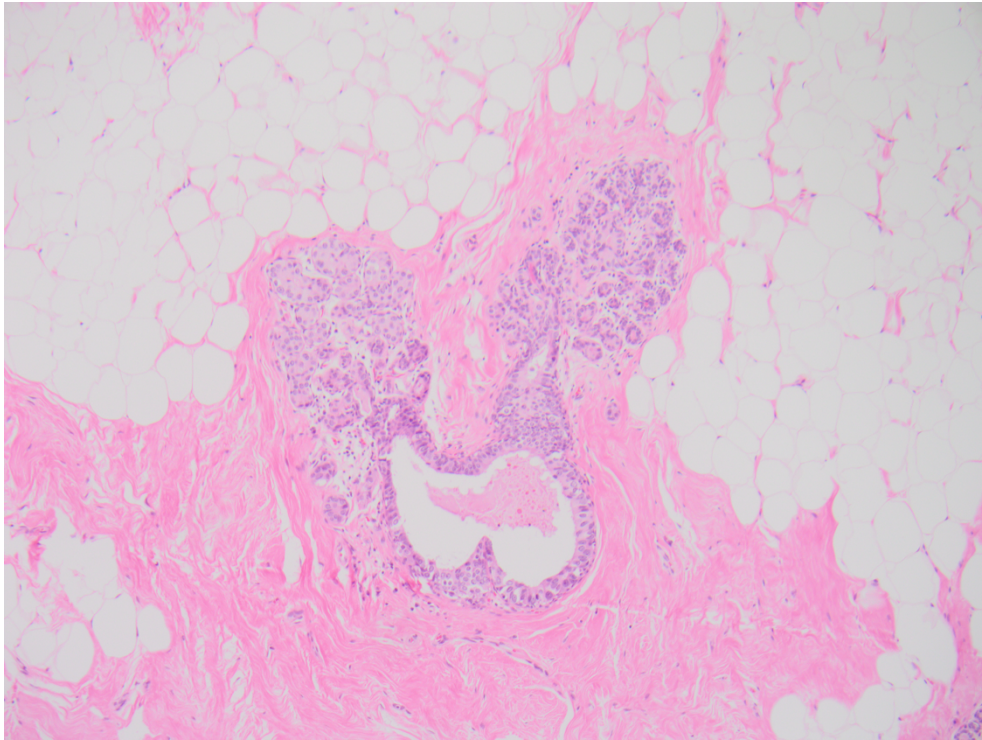


Figure 1.8 Terminal Ductal Lobular Unit infiltrated by Ductal Carcinoma in-situ

Note: H&E stained High Power (x10) slide demonstrating a TDLU with DCIS stained purple, kindly donated by Dr Tim Muriagu Consultant Histopathologist, Morriston Hospital, Swansea.

1.2.3.2 Lobular Carcinoma In-Situ

Lobular neoplasia (LN) describes the spectrum of lesions that originate in the terminal ductal lobular unit of the breast (Figure 1.5). LN comprises proliferative lesions that are classified according to the cellular changes ranging from atypical lobular hyperplasia (ALH) to lobular carcinoma in situ (LCIS) (Schnitt et al., 2022; Sokolova & Lakhani, 2022). LCIS is subclassified into classical, pleomorphic, and florid LCIS (Tan et al., 2020). The presence of LCIS is associated with a 7 to 10 fold increase in breast cancer risk when compared with the general population (Chuba et al., 2005; King et al., 2015; Rakha & Ellis., 2010; Schnitt et al., 2022), and are reported to be present in approximately 90% of classic lobular breast cancer specimens (Abdel-Fatah et al., 2007), suggesting that these lesions may be precursors of ILC (Abdel-Fatah et al., 2008).

Studies have shown that the classic and pleomorphic type of LCIS can be associated with mammographic calcifications (Georgian-Smith & Lawton, 2001). The presence of extensive calcification can result in discordant tumour size assessment between

DBT and MRI imaging when compared with final pathology measurement (Holland & Hendricks, 1994).

1.3 CLINICAL FEATURES OF INVASIVE LOBULAR CARCINOMA OF THE BREAST

1.3.1 Demographics

The incidence of breast cancer continues to rise steadily throughout the world, with annual increases of around 3% (Bray et al., 2018). The age of presentation varies with ethnicity, typically presenting at a younger age in Asian women, 40 to 50 years of age, compared with 60 to 70 years in their Western European counterparts (Leong et al., 2010; Li et al., 2002). Population studies have found that ILC is more common in older patients (Li et al., 2005). A prospective study of 12,206 patients registered in 15 international breast cancer study groups between 1976 and 2002, found that patients with ILC (6.2% of the cohort) were generally older than those with IDC (Pestalozzi et al., 2008). A large retrospective cohort study of almost 43,000 women also found a statistically significant difference ($p < .001$) in the age of patients with IDC compared with those with ILC, with mean age of 57 to 63 years respectively (Oesterreich et al., 2022). Although several retrospective studies performed in the 1990's did not find any age difference between the groups, the low cohort numbers and study era may have been confounding factors (Winchester et al., 1998; Yeatman et al., 1995). Interestingly, a recent retrospective observational analysis of the age and incidence of ILC in Ontario, reported an overall increase in the incidence of lobular cancer and a lowering of age at presentation (Findlay-Shirras et al., 2020). The authors commenting that although the use of combined hormone replacement therapy (cHRT) fell during the experimental period as the incidence of ILC rose, factors such as improved detection and diagnostic accuracy may account for the increase seen in the study period (Findlay-Shirras et al., 2020).

1.3.2 Risk Factors

The pathogenesis of breast cancer remains a subject of research. Despite the heterogeneity of breast cancer, there are several common risk factors. Globally, the estimated risk of developing breast cancer in females is 1 in 8 (Sung et al., 2021). The incidence of breast cancer in the Western World continues to rise, in part due to the improvements in the detection of small and preinvasive lesions. Although there has been an increase in incidence, mortality rates have decreased through the intervention of early diagnosis and targeted treatment. A recent observational cohort study in England assessing the outcomes of 512,447 women registered with early breast cancer, found a reduction in mortality rate of over 60% (Taylor et al., 2023).

Other recognised risk factors include environmental factors, family history, genetic predisposition, reproductive factors such as early menarche and late menopause, late age of first birth, and nulliparity. Lifestyle factors such as excessive alcohol, smoking, and dietary fat intake have all been shown to increase the risk of breast cancer (Sun et al., 2017). The risk of exogenous oestrogen has been evaluated in several studies. A recent meta-analysis of The Million Women Study (Beral, 2003) and The Collaborative Group of Hormonal Factors in Breast cancer (1997) found an increase in risk with cHRT (Chlebowski & Aragaki, 2023). The increased risk of ILC with cHRT is well documented in the literature (Li et al., 2003).

A recent nested case control study analysed data from Primary Care in the UK assessing breast cancer risk for current users of combined, or progesterone-only contraception, found only a slight increased risk for both types of contraception with an excess risk of 0.008% in 16-20 age group, and 0.265% in 39- 45 group (Fitzpatrick et al., 2023). This highlights the difficulties encountered when advising individuals on risk, as breast cancer is multifactorial with an interplay of genetic and environmental factors.

1.3.3 Diagnostic Evaluation

Screening programmes have improved outcomes for breast cancer through early detection (Taylor et al., 2023). However, cancers are also detected outside these

programmes in patients with breast symptoms who are not within the age range invitation, or as interval cancers (between screening years). Patients diagnosed in screening are recalled for assessment if an abnormality is noted on the mammogram. Individuals with a breast symptom are seen in symptomatic clinics. Clinical examination, ultrasound and mammography is undertaken with an image guided biopsy performed of any lesion found. This workup, referred to as ‘triple assessment’, improves diagnostic reliability, reducing the risk of incorrect diagnoses (Karim et al., 2020). Since the concept was first described in the late 1970’s, it has become the blueprint for diagnostic evaluation in breast clinics (Dixon et al., 1984).

The clinical findings alongside the imaging and pathology are reviewed and discussed in the multidisciplinary team (MDT) meeting. If the decision is for upfront surgery, the patient’s suitability for conservative surgery is considered. This is dependent on several factors. Tumour to breast size ratio needs to be carefully considered, even with current oncoplastic techniques, to ensure satisfactory cosmesis. For patients diagnosed with a lobular breast neoplasm who are planned for conservative breast surgery, MRI is requested for evaluation of tumour size, extent, and to excluded bilaterality.

1.3.4 Tumour Staging

The TNM staging system is a method of tumour classification that is internationally recognised. In the original breast classification, the parameters referenced were tumour size (T) (Table 1.1), lymph node status (N) (Table 1.2) and the presence of metastatic disease (M).

Table 1-1 Tumour Size in the TNM Classification

| Tumour (T) | Tumour Size mm |
|------------|----------------------------------------------------------|
| T1a | 1-5 |
| T1b | 6-10 |
| T1c | 11-20 |
| T2 | >20-50 |
| T3 | >50 |
| T4 | Involving skin, chest wall, includes Inflammatory cancer |

Note: TNM classification breast tumour size performed preoperatively

The lymph node status is further defined by the number and anatomical position of the involved nodes (see Table 1.2). Breast TNM staging can be assessed preoperatively (clinical prognostic staging) or postoperatively (pathologic prognostic staging).

Table 1-2 TNM Classification of Nodal Status Breast Cancer

| TNM Nodal Status | |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nx | Unable to classify |
| Nitc | Isolated tumour cells in node <0.2mm |
| Nmic | Micrometastatic deposit 0.2 – 2mm in size |
| N1 | Mobile nodes to ipsilateral level 1 or 2 axillary nodes |
| N2a | Fixed level 1 or 2 ipsilateral axillary nodes |
| N2b | Ipsilateral internal mammary chain nodes involved with no axillary nodes |
| N3 | Ipsilateral internal mammary chain, or ipsilateral infraclavicular nodes with level 1/2 ipsilateral axillary nodes, or ipsilateral supraclavicular fossa nodes |

Note: Abbreviated TNM classification of nodal status

The 8th Edition of the TNM staging system has incorporated tumour grade, *ER*, *PR*, *HER2* expression and/or amplification with anatomical staging (Giuliano et al., 2018). Additionally, the American Joint Committee on cancer (AJCC) has introduced the Oncotype genomic testing recurrence score for inclusion into the prognostication process (Hortobagyi et al., 2018). However, the benefit of this has yet to be fully validated, with some studies suggesting that the addition of the genomic score is of limited value, with less than 1% of the tumours being downstaged (Yoon et al., 2019).

1.3.5 Prognosis and Metastatic Spread

ILC is a special type of breast cancer incorporating differing subtypes as discussed above (section 1.2.3.2). In general, older studies suggested that classical lobular cancer had a similar prognosis to IDC NOS. Although, the pleomorphic subtype, with a lower *ER* positive rate and higher incidence of *HER2* positivity, has been shown to have a worse prognosis (Adachi et al., 2016; Rakha et al., 2013). However, Oesterreich and her team (2022) comparing the clinicopathological features of ductal and lobular cancers, noted that although disease free survival (DFS) was similar for both tumour types, overall survival (OS) was worse in the lobular cohort after 10 years of follow-up. The authors also assessed the effect of *PR* negativity and found no association with

a reduction in DFS. Similar survival outcomes for patients with ILC and IDC were noted in a retrospective cohort study, with these authors noting that pleomorphic and/or hormone receptor negative lobular tumours were associated with a higher rate of relapse and mortality (Yang et al., 2020).

Following a diagnosis of lobular carcinoma of the breast, recurrent disease can occur many years after the date of diagnosis (Oesterreich et al., 2022). The most common sites of metastatic spread of IDC and ILC are bone, lung, liver, and brain. However, there are differences between the two main types of breast tumours. Lung and liver metastases are more common in ductal than lobular cohorts, with figures of 51.9% and 23.9% respectively quoted in the literature (Inoue et al., 2017; Mathew et al., 2017). There is also a propensity for ILC to metastasise to less common anatomical sites such as the gastrointestinal tract, leptomeninges, peritoneum and ovaries (Arpino et al., 2004; Inoue et al., 2017; Korhonen et al., 2013; Pestalozzi et al., 2008). These differences are thought to be partly due to *CDHI* mutations associated with ILC.

1.4 THE EVOLUTION OF MAMMOGRAPHY

Mammography is currently the primary imaging technique in breast cancer screening and diagnosis (Moss et al., 2015; Tàbar et al., 2011). The detection of findings such as a mass, calcifications, architectural distortion, and asymmetry in both the symptomatic and asymptomatic patient, is part of the diagnostic work up, as these imaging features are often indicators of breast cancer (Section 1.5.1). Firstly, it is worth exploring the evolution of mammography, and the effect of the newer technologies on detection and assessment of breast cancer in general before discussing imaging for lobular cancer.

1.4.1 Screen-Film Mammography

With few advances in primary prevention, early detection is an important factor in improving breast cancer mortality rates. Implementation of screening mammography is one element that has had a positive impact on breast cancer survival rates (Feig, 2014). However, there is debate on how much benefit screening has had on mortality

rates. Results from the early large trials in Europe and USA, suggested a reduction in breast cancer mortality following the inception of screening with analogue/screen-film mammography (SFM) (Pisano et al., 2005; Tabár et al., 2003). A systematic review in 2015 (Myers et al) assessing the benefits and harms of screening, and a similar study evaluating the evidence from trials in Europe (Zielonke et al., 2020), also concluded that breast screening reduces mortality rates by at least 20% (Independent UK Panel on Breast Cancer Screening., 2012. Tabár et al., 2011). However, there is still ongoing debate regarding the benefit of mammographic screening programmes with recognised concerns over the harms of overdiagnosis (Evans & Vinnicombe, 2017).

As digital technology was introduced into general medical imaging, researchers considered the potential benefits in breast screening and assessment. The recognised limitations of SFM concerning sensitivity and specificity, especially in younger women, and in patients with dense breast tissue, coupled with practical issues surrounding image storage, degrading of images over time, difficulty with transferring image information and artefacts, highlighted the need to explore whether full field digital mammography (FFDM/DM) was the answer. With time, the imaging has become known as digital mammography, so will be referred to as DM when referenced.

1.4.2 Digital Mammography

The evolution of digital technology has revolutionised many aspects of medicine, and its introduction into breast screening and assessment has resulted in tangible benefits, along with some significant challenges. The change from film (analogue) screening to digital has been one that has been carefully considered and evaluated in large, multinational randomised controlled trials (RCT's) conducted to assess the effectiveness of a change of practice (Tabár et al., 2011). It was expected that the introduction of DM would improve the breast cancer detection rate (CDR). Initially, the large prospective multi-centre trials found that cancer detection was similar for both SFM and DM (Pisano et al., 2008; Tabár et al., 2011; Van Luijt et al., 2013). This may have been the result of the lower specificity of DM compared with SFM, in addition to confounding issues such as recall rate increases and the use of computer

aided detection (CAD), such that only a few of the initial landmark trials showed statistical significance benefit towards DM (Blanks et al., 2019; Del Turco et al., 2007; Pisano et al., 2005). Subgroup analyses from the landmark trials did however demonstrate improvements in cancer detection rates with DM in three groups of women: those with dense breasts, patients under the age of 50, and in pre- and perimenopausal women (Pisano et al., 2008; Skaane et al., 2007). A retrospective analysis of prospectively collected data from the UK screening programme between 2009 to 2010 and 2015 to 2016, concluded that the introduction of DM had resulted in a higher CDR of approximately 14% when compared to SFM (Blanks et al., 2019).

However, it is recognised that the cancer detection rates for both SFM and DM are limited in dense breast tissue although improved with DM, owing to an increase in contrast-resolution (Pisano et al., 2005; Skaane et al., 2007), can still be as low as 36-70% (Tabár et al., 2011; Wanders et al., 2017). The relatively low specificity of digital screening mammography, especially in dense tissue, results in unnecessary recalls for further views and an increased risk of missed cancers, both potentially a consequence of dense and overlapping breast tissue (superimposition) ((Pisano et al., 2005; Skaane et al., 2007). Technological advances in digital imaging led to the development of quasi three-dimensional breast imaging known as digital breast tomosynthesis (DBT), with the potential to improve diagnostic accuracy, even in dense breast tissue.

1.4.3 Digital Breast Tomosynthesis

Tomosynthesis imaging was first utilised in radiology in the 1930's prior to the introduction of computerised tomosynthesis (CT). In the late 1990's, the development of flat-panel detectors with amorphous selenium, silicon and cesium-iodine advanced the potential of this technology (Dobbins., 2009; Niklason et al., 1997). This, coupled with the refinements in digitalisation, resulted in the first commercially available unit being manufactured by Hologic in 2011. Following the results of a study reviewing the use of breast tomosynthesis on phantoms and mastectomy specimens, the concept of tomosynthesis imaging for the breast became established (Nikalson et al., 1997).

Digital tomosynthesis is an imaging technology where multiple low radiation dose images are taken of the breast and then reconstructed using algorithms producing

parallel image planes through the breast in approximately 1mm slices. The set of projection images are processed using reconstruction algorithms to produce a quasi 3D image of the breast. These slices reduce anatomical noise by limiting fibroglandular tissue overlap and this results in an improvement in lesion detection as the margins of lesions are highlighted (Roth et al., 2014).

Many of the initial studies comparing the performance of tomosynthesis with digital mammography were conducted retrospectively, reimaging patients with known cancers (Michell et al., 2012). This introduced a potential selection bias, and although the CDR and positive predictive rates were higher than 2D mammography, further research was needed to compare the two technologies. A recent systematic review and meta-analysis of 25 studies from both symptomatic and screening populations across the globe, concluded that sensitivity and specificity rates for cancer detection with tomosynthesis were 0.9 and 0.9 respectively, compared with 0.76 and 0.83 for digital mammography (Ko et al., 2021).

1.4.3.1 DBT Studies in Screening Population

There have been many studies to date assessing the use of tomosynthesis in screening. The results from most of the prospective and retrospective trials in Europe and USA trials suggest that the introduction of DBT has improved CDR and reduced recall rates (RR), with increases in detection of up to 30% (Ciatto, et al., 2013; Friedewald et al., 2014; Gilbert et al., 2015; Haas et al., 2013; Lång et al., 2015.; Rose et al., 2013; Skaane et al., 2013). The only RCT that demonstrated a non-significant (0.5%) increase in cancer detection rate was performed using a first generation tomosynthesis machine which was felt to be a confounding factor (Hofvind et al., 2019).

Large studies, mostly in the screening sector, have found that DBT, when compared with DM, has been shown to improve cancer visibility (Andersson et al., 2008; Michell et al., 2012; Rafferty et al., 2013), increase cancer detection rates (Bernardi & Houssami, 2017), reduce both unnecessary recalls (Gur et al., 2009; Hakim et al., 2010) and the need for additional mammographic views (Brandt et al., 2013; Hakim et al., 2010; Noroozian et al., 2012; Zuley et al., 2013). Interestingly, many investigators have noted that DBT improves the detection of architectural distortion (Caumo et al., 2018; Partyka et al., 2014; Yang et al., 2013), a recognised mammographic feature

associated with ILC (Section 1.5.1.2). Research has also suggested that the detection and assessment of ILC may be improved by DBT when compared with DM (Chamming's et al., 2017; Mariscotti et al., 2016).

1.4.3.2 DBT Trials in the Symptomatic Population

As the results of the large trials in screening populations suggesting that cancer detection rates and recall rates were improved with DBT, the technology was introduced into the diagnostic and symptomatic setting. Initial investigation into the performance of DBT in clinics also found that tomosynthesis improved margin analysis and lesion characterisation (Brandt et al., 2013; Hakim et al., 2010; Waldherr et al., 2013; Svahn et al., 2012; Tagliafico et al., 2012; Zuley et al., 2013). In the retrospective reader study by Svahn et al (2012), where 61.8% of the cohort had IDC, and 19.1% ILC, the CDR for all tumour groups was higher for DBT compared with DM. Many of the trials in the symptomatic and screening setting were conducted using both DM and DBT, resulting in an increase in radiation dose (Gennaro et al., 2018). This prompted the development of synthesised digital images reconstructed from the existing tomosynthesis slices to address the issue of excessive radiation.

1.4.4 Synthetic Digital Mammography

Technological developments have seen the introduction of a synthetic 2D view (s2D). These images reduce the radiation dose, acquisition time and interpretation time, when compared with standard DM (Svahn, 2015). The s2D images are created by adding and filtering the stack of reconstructed DBT slice dataset using manufacturer algorithms, with no increase in radiation dose (Freer et al., 2017). In addition, the algorithms can be formulated to identify sections that contain certain features, such as calcifications, masses, or architectural distortions, giving them extra weight as compared with surrounding glandular tissue, thereby highlighting them from the background (Horvat et al., 2019). The image is formatted and displayed as a conventional 2D mammogram in Digital Imaging and Communications in Medicine (DICOM) image. s2D received Food and Drug Administration (FDA) approval for use in combination with DBT in 2013 (Freer et al., 2017). To date, research with the latest s2D has suggested comparable sensitivity and specificity to standard DM when the

technology has been used in combination with DBT in screening populations (Gilbert et al., 2015; Skaane et al., 2014; Zuley et al., 2014), with some studies finding an increase in the CDR in the population screening with DBT and s2D compared with DM (Caumo et al., 2018; Caumo et al., 2021). As mentioned previously, the integration of manufacturer algorithms into the processing of the s2D images is designed to enhance the conspicuity of masses, calcifications, and architectural distortions, which may result in greater accuracy of tumour margin assessment and lesion measurement. This could potentially improve the preoperative evaluation of ILC. Research to date, however, has not studied the benefit of s2D with DBT in patients with ILC of the breast.

1.4.5 Contrast Enhanced Digital/Spectral Mammography

Contrast enhanced mammography (CESM) is a relatively new technology which has demonstrated higher sensitivity than standard mammography, especially in dense breast tissue, with sensitivities of 91-100% in the published literature (Pötsch et al., 2022; Sogani et al., 2021; Zamora et al., 2021). Digital imaging is enhanced by the addition of an assessment of tumour neovascularity using contrast agent after initial standard imaging to detect malignancy. Studies to date in the symptomatic setting have demonstrated significant improvements in both the sensitivity and specificity of cancer detection (Lalji et al., 2016; Lobbes et al., 2014). A meta-analysis by Tagliafico and colleagues (2016), confirmed the high sensitivity noted in the earlier studies but suggested a relatively lower specificity with CESM. This finding may have been due to the relatively small numbers in the study coupled with the lack of raw data in several of the papers included in the meta-analysis.

Studies have shown that preoperative tumour size assessment on CESM/CEDM demonstrates relatively good correlation with final pathology, with Pearson's correlation coefficients of 0.73 to 0.905 (Fallenberg et al., 2016; Lobbes et al., 2015). However, this technology, like MRI, can lead to overestimation of size by greater than 15mm. A prospective study of 102 subjects with 99 image sets, found that tumour overestimation by greater than 15mm was found in 11% of cases on CESM, compared with 24% on MRI (Sumkin et al., 2019). A recent single centre observational study

(Daniaux et al., 2023) comparing standard imaging with CESM and MRI, also concluded that the technology correlated with histological size and was also unaffected by breast density, with a higher positive predictive value compared with MRI, 72.0% and 42.5% respectively. A finding also noted by a study evaluating the extent of disease in newly diagnosed breast cancer patients (Lee-Felker et al., 2017).

An advantage of CESM in the preoperative setting is the detection of additional foci of disease, ipsilateral and contralateral. Evidence from trials have shown that the technology has similar sensitivity to MRI for demonstrating additional foci, although early research suggests that CESM has a higher positive predictive value when compared with MRI (Jochelson et al., 2013; Lee Felker et al., 2017). However, a small retrospective review of 30 patients with ILC who were assessed preoperatively with CESM and no MRI, found 6.67% required further surgery for involved margins (Patel et al., 2018).

1.5 IMAGING INVASIVE LOBULAR CARCINOMA

1.5.1 Digital Breast Tomosynthesis

Published studies have consistently shown that the introduction of DBT has improved cancer detection rates and reduced recall rates when compared with digital mammography, such that tomosynthesis is now an accepted imaging modality in breast screening (Ciatto et al., 2013; Friedewald et al., 2014; Gilbert et al., 2015; Marinovich et al., 2018; Rafferty et al., 2013; Skaane et al., 2013). This data resulted in the technique being introduced into the symptomatic community, as the 3D imaging resulted in higher specificity than standard 2D imaging. One multicentre trial of all tumour subtypes assessed the use of DBT in the preoperative assessment of a group of 166 patients (Fontaine et al., 2019). The authors found that although the addition of tomosynthesis to standard imaging with DM improved the detection of additional foci of disease and contralateral disease, especially in non dense breast tissue, DBT had lower sensitivity than MRI.

Although detection is important in diagnosing breast cancer both in the screening and symptomatic sector, accurate assessment of tumour size in the preoperative setting is

essential in planning the primary treatment. The measurement of the main tumour mass along with exclusion of multifocality, multicentricity and bilaterality is essential in the surgical planning of all breast patients. Tumour size evaluation with the standard imaging tools, including DBT and USS can be problematic for several reasons. Regarding mammography in general, “Anatomical noise” can contribute to a lower sensitivity, where normal anatomy obscures the point of interest in a radiological image (Cederström & Fredenberg., 2014). This effect is more pronounced in dense breasts due in part to overlap of fibroglandular tissue (Van Goethem et al., 2004), which is improved by the quasi-3D images achieved with tomosynthesis (Roth et al., 2014). In addition, the frequency of recalls is also reduced due to the technology as it lessens summation shadowing (Peppard et al., 2015).

Preoperative assessment can be more challenging in patients with ILC of the breast. The more diffuse growth pattern of lobular cancers can result in difficulty with detection and assessment of tumour size and, in addition, in identifying the presence of multifocality on imaging (Arpino et al., 2004; Pestalozzi et al., 2006). Imaging features of lobular tumours on mammography can be varied, and the lesion has a higher propensity for being occult on mammography when compared with other subtypes of cancer (Mariscotti et al., 2016). In these early studies, the risk of diagnosing contralateral disease was 20.9% in cases of ILC, compared with 11.2% for IDC (Arpino et al., 2004). However, data from a more recent UK study (Langlands, et al., 2016), found that there was no statistically significant increase in synchronous contralateral disease in an ILC cohort compared with ductal tumours.

The most common mammographic findings of lobular cancers are masses, architectural distortions, or asymmetries, features which are discussed in more detail below.

1.5.1.1 Mass

Breast cancer is often seen as a mass on mammography. These masses can be well defined, ill defined or spiculated (Figure 1.9). Tomosynthesis technology has enhanced margin delineation, which has translated into greater sensitivity and specificity for defining whether a lesion appears malignant, as the visualisation of the edges of masses are more enhanced (Helvie., 2010). Consequently, detection, evaluation, and

measurement of tumours with distinct margins has been improved with DBT (Mariscotti et al., 2016; Roth et al., 2014). However, ILC is rarely seen as a well-defined rounded lesion, more often appearing as a spiculated or ill defined mass (Johnson et al., 2015; Michael et al., 2008) (Figure 1.9).

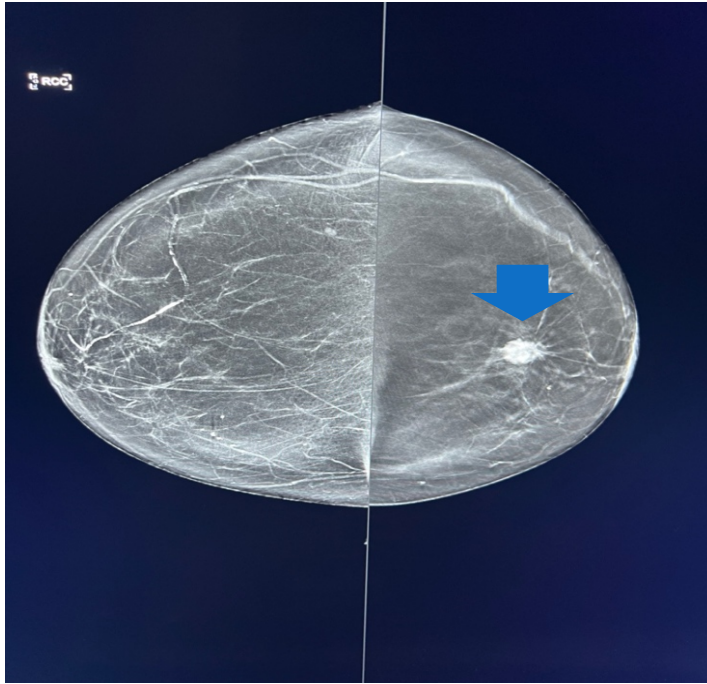


Figure 1.9 Tomosynthesis image of a spiculated mass
Note: Left breast lesion confirmed on biopsy as Grade 2 ILC. Image from HDUHB collection.

1.5.1.2 Architectural Distortion

The descriptor architectural distortion (AD) refers to a mammographic finding where there is a suggestion of a dimpling in the image with no obvious mass lesion present (Sickles et al., 2013). As tomosynthesis reduces tissue superimposition, the appearance of AD is often more evident with this technology (Dibble et al., 2018; Durand et al., 2016). Studies have shown that tomosynthesis has improved the detection of AD (Bahl et al., 2017; Dibble et al., 2018; Durand et al., 2016; Grubstein et al., 2016; Mariscotti et al., 2016; Partyka et al., 2014; Skaane et al., 2012). A distortion that is seen on mammography is often caused by benign breast conditions such as postoperative changes, radial scars, fat necrosis and complex sclerosing lesions which have several aetiologies. However, sometimes it is the only indication of a malignant process on imaging. Indeed, a systematic review and meta-analysis concluded that the pooled positive predictive value of malignancy for AD on DBT was 34.6% (Choudhery et al,

2021). A recent retrospective review also found that distortion noted on tomosynthesis was associated with a 30% malignancy rate, highlighting the importance of assessing these lesions (Romanucci et al., 2023).

Although the most common mammographic imaging finding is an ill defined mass, lobular cancers can also be seen as an AD on mammography. An imaging feature of ILC that is more appreciated on tomosynthesis than standard mammography (Bane et al., 2005; Caumo et al., 2018; Chamming's., et al, 2017; Grubstein et al., 2016; Lopez and Bassett, 2009; Moore et al., 2000; Partyka et al., 2014; Yang et al., 2013). The size assessment of an area of distortion is often underestimated by mammography (Partyka et al., 2014). (Figure 1.10). This can be partly explained by the difficulties in delineating the margins of the lesion.

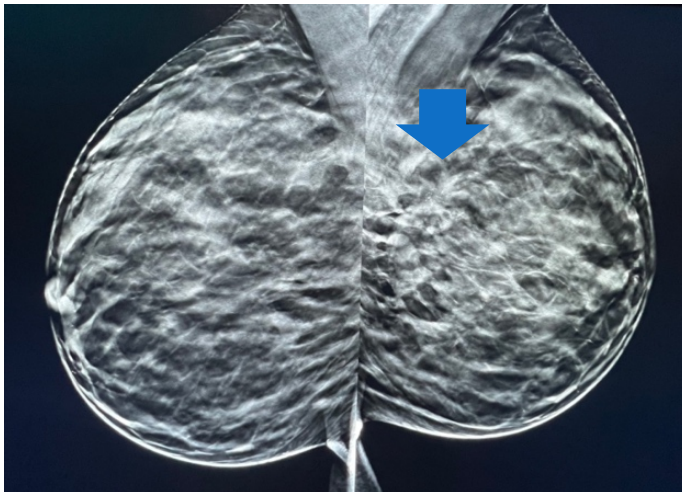


Figure 1.10 Tomosynthesis image of an area of architectural distortion
Note: DBT left MLO images illustrating architectural distortion (blue arrow) associated with a few microcalcifications due to ILC left breast. Image from HDUHB collection.

1.5.1.3 Asymmetry

An asymmetry on mammography is a vague area of density seen in less than one quadrant of a breast, and, which is only seen on one of the two mammographic views, CC or MLO (Sickles et al., 2013). Most asymmetries are due to superimposition of breast tissue referred to as “summation shadow” or “summation artifact” (Johnson, 2021). A developing asymmetry, however, is a new or increased area of breast density, and this mammographic feature is associated with a higher risk of malignancy (Chesebro et al., 2016; Leung & Sickles, 2007; Price et al., 2015). In a recent review

of 2,230 mammograms of interval and screened cancers, asymmetry was found to be the predominant imaging feature associated with missed cancers on screening mammography (Hovda et al., 2023). Studies suggest that because tomosynthesis reduces summation, the technology has improved the evaluation of asymmetry (Bernardi et al., 2012; Freer et al., 2017). Tomosynthesis technology produces multiple low radiation dose images through the breast, reducing the effect of tissue overlay, such that asymmetries which are related to the summation of normal glandular tissue are reduced. This has been shown to reduce the number of false positive recalls in screening (Lourenco et al., 2015). Although the most common mammographic abnormalities associated with a lobular cancer is a mass or architectural distortion, ILC can present as a developing asymmetry on mammography (Chamming's et al., 2017; Lopez & Bassett, 2009; Mariscotti et al., 2016).

1.5.1.4 Calcifications

Calcification on mammography is caused by calcium deposits within the breast. They are radio-opaque on imaging, appearing as white flecks. Most calcifications are caused by benign conditions (Horvat et al., 2019). The morphology of the calcification seen on imaging is used to predict the risk of malignancy. Breast calcification maybe the only sign of early breast cancer on mammography and is seen in approximately 50% of mammograms (Gajdos et al., 2002; Mordang et al., 2017).

Early research evaluating the detection of microcalcifications comparing digital mammography and DBT, had mixed results; some studies demonstrating a lower sensitivity for tomosynthesis (Spangler et al., 2011; Tagliafico et al., 2015), and others concluding that DBT was at least as good as standard 2D mammography in the detection and assessment of calcification (Destounis et al., 2013; Kopans et al., 2011). With the addition of synthetic 2D views and algorithmic tomosynthesis upgrades that enhance depiction of calcification, the detection on DBT has improved (Hwang et al., 2018; Mariscotti et al., 2017; Sidkley et al., 2009).

Research suggests that calcifications are found less frequently in ILC when compared with IDC (Hilleren et al., 1991; Krecke & Gisvold, 1993; Le Gal et al., 1992; Porter et al., 2014; Sickles, 1991). However, many of these studies were performed with screen film mammography, limiting generalisation. Calcification associated with ILC is more

common in the presence of a DCIS or LCIS component (Rakha & Ellis, 2010) (Figure 1.11), as discussed in Section 1.2.3.

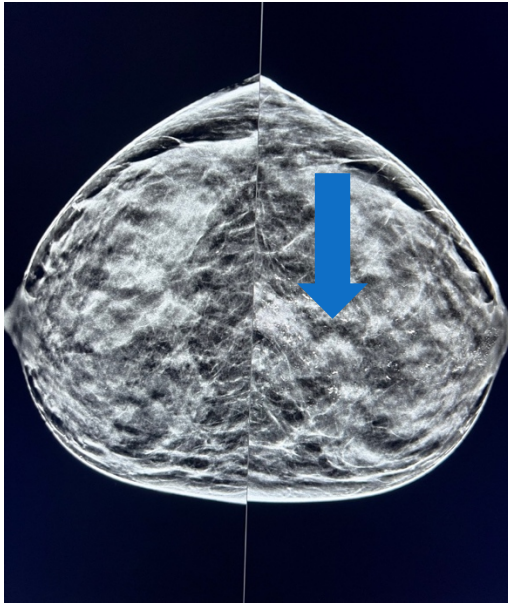


Figure 1.11 Lobular cancer associated with widespread microcalcification.

Note: DBT C-view CC image left breast demonstrating asymmetrical densities with microcalcifications. Final pathology confirmed multifocal ILC with widespread LCIS. Image from HDUHB collection.

1.5.2 Sonography

Early studies assessing the use of breast sonography demonstrated relatively poor correlation with tumour size, especially in the presence of a large intraductal component (Gruber et al., 2013; Luparia et al., 2013). However, advances in technology have improved image resolution and rapid processing of breast ultrasound, such that it is one of the mainstay imaging tools for assessment, detection and image-guided biopsy of disease noted both on MRI and DBT. Reported sensitivities of tumour detection on US in the literature range from 68 to 98% (Dillon et al., 2006; Munot et al., 2012; Paramagul et al., 1995; Porter et al., 2014; Rebolj et al., 2018; Selinko et al., 2004. Skaane & Skjorten, 1999). However, currently breast sonography is not considered a stand-alone screening modality.

BI-RADS 5th Edition Atlas (Sickles et al., 2013) standardises the reporting of sonographic findings by defining the appearances of lesions. The lexicon includes shape, orientation, margin, echo pattern and posterior acoustic effects, to stratify risk of malignancy (Sickles et al., 2013). The orientation of a lesion can be described as

horizontally or vertically orientated, with the latter finding more common in malignant lesions. The posterior effect refers to shadowing or brightness of the tissue below the lesion, with the former more commonly associated with cancer (Weinstein et al., 2004). The echo pattern describes the appearance of the lesion in relation to the surrounding tissue, hypoechoic being darker than, hyperechoic brighter and isoechoic similar to the background pattern.

Lobular cancers are often seen as a vague hypoechoic mass on sonography with irregular borders and posterior acoustic shadowing, features that can be difficult to measure accurately (Figure 1.12). Studies show that ultrasound significantly underestimates tumour size in patients with ILC (Brem et al., 2008; Gruber et al., 2013; Munot et al., 2002; Nonnemacher et al., 2023; Wang et al., 2014). However, the literature suggests that this technology is better than DBT at detecting additional foci of disease when the breast is reassessed with ‘second-look’ imaging following breast MRI (Kim et al., 2016; Mariscotti et al., 2015).



Figure 1.12 Hypoechoic mass with posterior acoustic shadowing on sonography.

Note: Biopsy confirmed a right breast ILC Grade 2 seen on ultrasound as a mass with irregular margins and posterior acoustic shadowing. Image from HDUHB collection.

1.5.3 Magnetic Resonance Imaging

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a tool that is indicated in several clinically defined situations in the management of breast cancer. Recognised indications include preoperative staging, assessment of breast implant integrity, screening high-risk individuals, evaluation of the breast for tumours that are occult on standard imaging, and to assess response to neoadjuvant chemotherapy

(Mann et al., 2019). For breast cancer detection, studies have demonstrated sensitivity rates of up to 93%, and specificity rates of 71% (Zhang et al., 2016). Additionally, as MRI evaluates neovascularisation, it is less affected by breast density than the other imaging modalities (Mann et al., 2022).

Preoperative Breast MRI is performed to assess tumour size, and to evaluate the extent of disease by detecting multifocality in the ipsilateral breast. In addition, it helps to exclude contralateral breast lesions in a patient planned for conservative surgery, with early studies suggesting that the routine use of preoperative imaging by MR in all tumour groups reduced re-excision rates by up to a third (Berg et al., 2004; Bedrosian et al., 2003). Although it is recognised that MRI is superior to standard breast imaging tools, such as mammography and sonography, studies consistently demonstrate that MRI can overestimate disease, especially with lobular pathology (Houssami et al., 2008; Mann, 2010; Parvaiz et al., 2016). This has resulted in an increase in mastectomy rates with no evidence of an effect on recurrence or survival rates (Bleicher et al., 2009; Houssami & Hayes, 2009; Morrow, 2008; Sardenelli et al., 2021; Solin et al., 2008). It was felt that some of these findings may have been confounded by patient factors, as many of the studies were heterogenous. However, the COMICE trial, a UK based RCT of 1625 women planned for conservative breast surgery, assessing the effect of preoperative MRI on re-excision rates, also reported similar findings (Turnbull et al., 2010). A systematic review and meta-analysis published in 2022 also concluded that MRI imaging increases mastectomy rates, with no evidence of an effect on DFS (Li et al., 2022). It is worth noting that many of the patients in these trials investigating the use of MRI, were imaged with digital mammography and not tomosynthesis. A large trial reviewing the benefit of additional MR imaging in the preoperative assessment of DM and DBT screened patients, found that the detection of additional foci noted on MRI had limited impact, especially in less dense breast tissue (Chudgar et al., 2017).

MRI of the breast can be useful in the assessment of patients with dense breast tissue. As discussed in Section 1.1.2.1, dense parenchyma is a recognised independent risk factor for breast cancer, conferring a 1.8-6 times increased risk when compared with patients with fatty involuted breast tissue (Boyd et al., 2006; Boyd et al., 2007). A recent non-randomised retrospective study in the UK, reviewed the selective use of breast MRI in patients with dense breast tissue with newly diagnosed ILC and

concluded that employment of this risk stratification resulted in an improvement in sensitivity and specificity (Bansal et al., 2016). This study compared standard DM, not tomosynthesis, with breast MRI. However, DBT has demonstrated a higher breast cancer detection rate than standard DM in mixed to moderately dense breast tissue (BI-RADS B & C/2 & 4) in a screening cohort, which may translate into an even greater benefit in the evaluation of patients with dense breast tissue and ILC detection and assessment (Gilbert et al., 2015; Houssami & Turner, 2016; Pertuz et al., 2016; Rafferty et al., 2016). A more recent study reviewing the use of preoperative MRI in all cancer subtypes concluded that in dense breast tissue, the investigation increased diagnostic uncertainty, resulting in more biopsies with no increase seen in CDR (Onega et al., 2022). Additionally, a systematic review and meta-analysis found that the routine use of preoperative MRI in all tumour groups increased the risk of ipsilateral and contralateral mastectomies (Houssami et al., 2017).

One rationale for the use of MRI in the preoperative evaluation of lobular cancers is the general held belief that there is a higher risk of contralateral disease in this subtype of breast tumour, with early studies suggesting that contralateral disease is more prevalent in patients with a diagnosis of ILC. However, one UK retrospective study, reviewing breast cancer cohort outcomes between 1998 and 2003 of both ductal (n=32,735) and lobular cases (n=5,397), concluded that there was no significant difference in the incidence of bilateral disease in the two histology groups. The authors proposed the idea that the use of preoperative MRI should be restricted to patients undergoing breast conservative surgery (Langlands et al., 2016). However, a more recent retrospective analysis performed in the USA, found that MRI detected contralateral disease in 3% of the ILC cases, suggesting that preoperative MRI should be considered in all patients with ILC (Cocco et al., 2021). This may be a reflection of different working practices in the two countries.

However, it is widely acknowledged that MRI of the breast is a highly sensitive imaging modality that is indicated in clinically defined situations. In the UK, preoperative MR breast imaging is performed in patients who have been diagnosed with a lobular cancer of the breast when the individual is planned for conservative breast surgery, rather than mastectomy. Evidence from early trials found that MRI reduced re-excision rates by up to a third, as it detected additional foci of disease, both

in the ipsilateral and contralateral breast that was occult on routine imaging, such that definitive surgery was possible from the outset (Berg et al., 2004; Bedrosian et al., 2003). Additionally, MRI is currently the most accurate imaging modality for preoperative tumour size assessment, although over and underestimation is seen in up to 15% of cases (Girometti et al., 2020).

However, the evidence is conflicted as MRI has the potential to delay surgery and increase mastectomy rates with no added benefit to the patient with regard to survival (Bleicher et al., 2009; Houssami et al., 2008; Sardanelli et al., 2022). Data from a large UK based trial in 2010 found no benefit in the assessment in patients with ILC in the cohort randomised to preoperative MRI of the breast (Turnbull et al., 2010). Of note, this trial and others assessing the benefit of breast MRI, used DM as comparator.

Studies evaluating the use of breast MRI in the preoperative evaluation of lobular cancer, have found that the imaging improved tumour size assessment when compared with mammography with most suggesting that the imaging did not result in an increase in mastectomy rates (Fortune-Greeley et al., 2014; Lobbes et al., 2017; Mann et al., 2008; Mann, 2010). In the UK, preoperative breast MRI is performed on patients who have been diagnosed with ILC, and who are planned for conservative breast surgery, to assess disease extent in the ipsilateral breast and to exclude contralateral disease. MRI has high sensitivity for detection of lobular breast cancer, with studies reporting sensitivities around 96% (Mann et al., 2008). However, it is well recognised in the literature that the tumoural growth pattern of lobular neoplasms causes less extensive proliferation of new vessels, an important feature in MRI imaging, such that the enhancements seen with malignancy can be more subtle with this type of breast cancer (Daniel et al., 1998; Lee et al., 1998). The typical MRI findings in patients with ILC are masses with circumscribed, irregular or spiculated borders, in addition to non-mass enhancements (Sickles et al., 2013) (Figure 1.13).

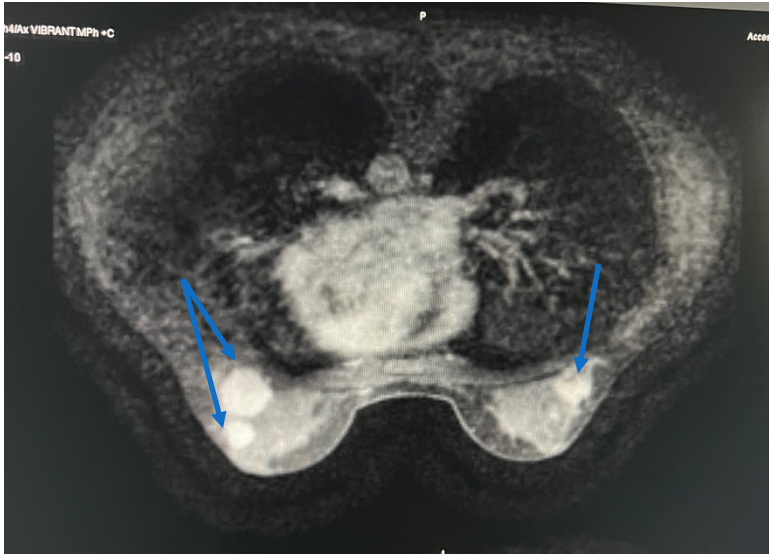


Figure 1.13 MRI Breast Bilateral Invasive Lobular Cancers

Note: Contrast-enhanced MRI both breasts demonstrating multifocal invasive lobular breast cancer in left breast, the largest lesion is 26 x 30mm in diameter, and an ill-defined unifocal right breast lobular cancer measuring 22mm with small foci of uptake. Pathology confirmed the imaging findings, with diffuse ILC in both breasts. Images from HDUHB library.

However, there are limitations with breast MRI. There are patient considerations such as body mass index, claustrophobia, or metallic implants. In addition, the procedure is time-consuming, requiring the use of contrast-enhancing agents, such that dedicated sessions to perform the procedure need to be planned, such that delays in time to surgery can occur with the potential to cause patient anxiety (Bleicher et al., 2009; Chandwani et al., 2014).

1.6 CLINICAL MANAGEMENT OF INVASIVE LOBULAR CARCINOMA

1.6.1 Preoperative Assessment

Screening studies have shown an improvement in cancer detection rates with the use of DBT as standalone or in combination with digital mammography, compared to DM alone (Ciatto et al., 2013; Friedewald et al., 2014; Gilbert et al., 2015; Rafferty et al., 2013; Skaane et al., 2013). Although detection is important, both in the screening and symptomatic sector, accurate assessment of tumour size and extent in the preoperative setting is essential in planning the primary treatment. The measurement of the main tumour mass along with exclusion of multifocality, multicentricity and bilaterality is essential in the surgical and oncological treatment planning of all breast patients. In theory, preoperative tumour size assessment should be improved with breast tomosynthesis when compared with digital mammography, and sonography, as lesion margins are highlighted with this technology. Several studies have evaluated the accuracy of DBT in tumour size estimation (Chamming's et al., 2017; Destounis et al., 2013; Förnvik et al., 2010; Girometti et al., 2018; Luparia et al., 2013; Mariscotti et al., 2014; Mariscotti et al., 2016; Mun et al., 2013; Seo et al., 2014; Timberg et al., 2010). Levels of agreement vary, with some studies demonstrating overestimation especially in dense breast tissue (Destounis et al., 2013), with others noting underestimation (Förnvik et al., 2010). DBT was found to be superior to DM and US both in the detection and evaluation of multifocality, with 66.4% level of concordance with final pathology size (Luparia et al., 2013). On subgroup analysis of this cohort, looking specifically at ILC, the correlation of tumour size on MRI with pathology, and DBT with pathology, was 0.93, and 0.90 respectively. However, Chamming's et al (2017) in a small retrospective study on 14 patients with ILC, found measurement on tomosynthesis significantly underestimated tumour size.

Most studies in the literature have published results on the size assessment of ductal cancer, with lobular tumours often assessed on subgroup analysis. This subtype has distinct clinicopathological features when compared with other breast cancer subtypes, which can lead to difficulties in detection and assessment on standard imaging. ILC is most often seen as a mass on mammograms, although it can present as an architectural distortion on mammography, an imaging feature that is more appreciated on

tomosynthesis than standard mammography (Bane et al., 2005; Chamming's et al., 2017; Lopez & Bassett, 2009). As the effect of tomosynthesis reduces tissue superimposition and enhances margin delineation, the introduction of DBT has improved detection of these distortions (Durand et al., 2016; Partyka et al., 2014). In addition, distortion is one of the most missed mammographic abnormalities in screening and diagnostic assessments, owing to subtle features on standard digital imaging (van de Veer et al., 2023) (Section 1.5.1.2). In addition, a recent systematic review and meta-analysis suggested that the risk of malignancy associated with a distortion detected on tomosynthesis, can be as high as 34.6% (Choudhery et al., 2020), confirming the importance of thorough assessment of these mammographic findings. Additionally, the edges of this particular imaging feature are difficult to measure, with studies suggesting that size assessment is often underestimated even with tomosynthesis (Caumo et al., 2018; Partyka et al., 2014; Yang et al., 2013).

The presence of calcification is often a useful mammographic finding, as the reviewer's eye is drawn toward the white flecks on an image. Most calcifications are caused by benign pathology and are less often found with lobular cancers (Hilleren et al., 1991; Krecke & Gisvold, 1993; Le Gal et al., 1992; Porter et al., 2014; Sickles, 1991), unless the ILC is associated with a preinvasive component (Rakha & Ellis, 2010). If the calcifications are not associated with a mass lesion, image guided sampling such as vacuum-assisted biopsy (VAB) is performed for histological confirmation.

Three studies to date have evaluated the use of DBT in the detection and characterisation of lobular tumours. Grubstein et al (2016) in a retrospective study on 23 patients, found that imaging features commonly associated with ILC, such as AD, were enhanced by DBT. Mariscotti et al (2016) in a multireader retrospective study concluded that imaging with tomosynthesis and DM improved the detection of multifocal disease and bilateral disease in patients diagnosed with ILC. Margin delineation, detection of distortion and asymmetry were all improved with the addition of DBT. The same group in a prospective study compared the accuracy of DBT in preoperative assessment with MRI, US, and DM, to assess tumour extent with all breast tumour types (Mariscotti et al., 2014). Although MRI had the highest sensitivity for cancer detection at 98.8%, compared with 90.7% with DBT and 85.2% with DM,

MRI did not improve surgical outcomes. Interestingly, this study found that preoperative assessment with DBT+DM+US resulted in comparable sensitivity to MRI at 97.7% (Mariscotti et al., 2014).

1.6.2 Surgical Management

Primary surgical treatment of early invasive breast cancer involves either mastectomy or breast conservation surgery with or without an oncoplastic technique. Breast conservation surgery is considered if excision of the primary lesion is possible with clear margins, if the patient is a suitable candidate for adjuvant radiotherapy (should this be needed), and if the envisaged final cosmetic result is acceptable to the patient (Kaufmann et al., 2006; Newman, 2017; Veronesi et al., 2002). The preoperative clinical and image evaluation of tumour size, extent and stage is important in planning the surgical intervention. The more accurate the assessment, the more appropriate the primary course of action.

As early studies suggested that rate of positive margins following breast conservation was greater for patients with ILC, with rates of compromised margins in the literature of up to 50% (Dillon et al., 2006; Fortunato et al., 2012; Moore et al., 2000), mastectomy was the operation of choice in this subtype. As evidence on the safety of conservation breast surgery in ILC became available, coupled with the use of preoperative MRI, reoperation rates are now much lower and comparable to those for IDC (Nanda et al., 2021; Veronesi et al., 2002).

1.6.3 Adjuvant Therapies

Following surgery for early breast cancer, decisions surrounding the use of adjuvant therapy such as chemotherapy, endocrine therapy, and radiotherapy, are informed by the results of the final histology, the receptor status, and the general health of the patient. The aim is to evaluate these factors in each patient to provide an individualised approach. Prognostic testing in the adjuvant setting is explored further in Section 1.7.

1.6.3.1 Chemotherapy

The use of adjuvant chemotherapy is recommended for patients at moderate to high risk of recurrence (Barnard & Klimberg., 2017). Breast cancer response to chemotherapy is generally greater in tumours that are high grade, with low hormone receptor statuses, and with high proliferative indices, such as *Ki-67* (Nielsen et al., 2021). Recent studies have found that approximately 90% of all lobular cancers are of the luminal subtype (Pramod et al., 2021; Sivadas et al., 2022), so these factors that can predict a good response to chemotherapy are often absent in patients with ILC (See section below on Luminal Breast cancers). Therefore, the response to neoadjuvant (primary) chemotherapy and adjuvant chemotherapy is generally lower in patients with ILC compared with IDC (Cristofanilli et al., 2005; Marmor et al., 2017). A study by Marmor et al (2017) assessed 10 year survival rates in women with ILC who had received adjuvant endocrine therapy with or without chemotherapy, found that after adjusting for age, tumour stage and treatment factors, there was no benefit from adjuvant chemotherapy. More recent meta-analyses have also concluded that the addition of chemotherapy in lobular patients did not result in a statistically significant improvement in survival in both the adjuvant (Davey et al., 2022; Trapani et al., 2021) and neoadjuvant settings (O'Connor et al., 2022). However, lobular cancers that are node positive, pleomorphic subtype, or those that overexpress *HER2*, should be considered for adjuvant chemotherapy as studies suggest an improved response to chemotherapy in these groups (Tamirisa et al., 2019).

1.6.3.2 Radiotherapy

The Early Breast Cancer Trialists Collaborative Group (2011) reviewed the evidence for adjuvant radiotherapy following conservative breast surgery concluding that the intervention reduces the risk of local recurrence in early breast cancer. Regarding radiotherapy in lobular breast patients, most of the trials did not differentiate between tumour types, such that is difficult to evaluate whether there is greater survival benefit in this type of breast cancer. However, postmastectomy radiotherapy is indicated if the tumour margin is less than 1mm, or if there is involvement of the skin, or axillary nodal positivity, or heavy burden of disease, as it has been shown to reduce the risk of local recurrence for all subtypes (Hewitt et al., 2022).

1.6.3.3 Endocrine Therapy

Endocrine therapy is indicated in breast tumours that are *ER* positive (see section 1.2.2 above). Studies have shown that the majority of ILC are Grade 2 *ER* positive cancers that are classified as luminal A subtype (Biglia et al., 2013; Ciriello et al., 2015; Li et al., 2005; Oesterreich et al., 2022; Rakha et al., 2013). Historically, Tamoxifen has been the drug of choice as adjuvant hormonal therapy treatment in breast cancer. With the advent of the Aromatase Inhibitors, and the trials that validated the use of these agents, these drugs are now standard endocrine therapy used in the adjuvant setting for most postmenopausal patients with breast cancer (Goldhirsch et al., 2007). The results of one of these studies, the BIG 1-98 trial, investigated the use of Letrozole, a non-steroidal Aromatase Inhibitor, against standard therapy, Tamoxifen, in the adjuvant setting (Metzger-Filho et al., 2015). This large RCT analysed a subset of patients with ILC and found that disease-free survival (DFS) was higher in the cohort prescribed Letrozole, 82% compared with 74% on Tamoxifen, a statistically significant finding (Metzger-Filho et al., 2015). To understand this effect, an in-vitro study evaluating the action of *ER* and Tamoxifen, found that lobular cell growth increased with Tamoxifen (Sikora et al., 2014). However, these results have yet to be confirmed in-vivo studies.

1.6.4 Neoadjuvant Therapy

The standard pathway for the management of most breast patients is surgery followed by adjuvant therapy. However, chemotherapy and endocrine therapy can be given prior to definitive surgery. This approach is termed neoadjuvant chemotherapy (NACT) or endocrine therapy (NET). Neoadjuvant treatment can help downstage disease to facilitate breast conservation surgery and/or to reduce axillary nodal involvement. Additionally, chemotherapy response can be used as a guide to prognosis and can inform decisions regarding adjuvant therapy (Hyder et al., 2021; National Guideline Alliance (UK), 2018). For *HER2* positive breast cancer or triple negative breast cancer (TNBC), there are established national guidelines for the use of NACT. However, a recent UK study found variation in the use of, and decisions surrounding, neoadjuvant therapy suggesting a need for improved guidelines and discussion in the MDT (Fatayer et al., 2022; Whitehead et al., 2021).

1.7 PROGNOSTIC TESTING IN INVASIVE LOBULAR CARCINOMA OF THE BREAST

1.7.1 Subtypes of Breast cancer

Breast cancer is a heterogenous disease encompassing different histological types and molecular subtypes. In general, around 70% of all breast tumours express *ER* and/or *PR* (Lim et al., 2012), with rates of *ER* and *PR* positivity as high as 90 and 70% respectively in lobular cancer (Arpino et al., 2004; Orvieto et al., 2008; Rakha et al., 2008) (Section 1.2.2). Molecular classification is generally based on receptor expression of oestrogen, progesterone and *HER2*, with the proliferation marker *Ki-67* (Ciriello et al., 2013). *HER2* is a transmembrane receptor that controls epithelial cell growth and differentiation. It is overexpressed in approximately 15-30% of all breast cancers (Burstein, 2005). *Ki-67* is an antigen which is a clinically validated marker that can be used to assess tumour cell proliferation (Lashen et al., 2023). A large systematic review and meta-analysis of 85 studies comprising 32,825 patients, found that elevated *Ki-67* is associated with poor survival (Davey et al., 2021; Stuart-Harris et al., 2008).

Molecular subtyping of tumours using gene expression microarray techniques has helped enhance the classification of breast cancer with seminal work by Perou et al (2000) pioneering the subclassification of breast cancer. With the use of DNA microarray technology, the authors proposed a classification of four molecular subtypes of breast cancer based on 49 intrinsic genes (Perou et al., 2000). Researchers in the pursuit of improving treatment and outcomes for patients, are uncovering the heterogeneity within each subgroup (Ciriello et al., 2013). This is especially true for invasive lobular cancer (Desmedt et al., 2016).

The Cancer Genome Atlas Network (2012) outline the main subtypes as described below.

1.7.1.1 Luminal A

Luminal A breast cancer account for approximately 60% of all breast cancers (Yersal & Barutca., 2013), and is distinguished by *ER* and/or *PR* positivity, the absence of *HER2* and low expression of *Ki-67* (Orrantia-Borunda et al., 2022) (Table 1.3 below).

However, studies are discovering that the classification luminal A includes a genetically heterogenous group of tumours (Ciriello et al., 2013). This is relevant in respect of lobular breast cancers, as the majority are classified as luminal A (Ciriello et al., 2013; McCart Reed et al., 2015).

1.7.1.2 Luminal B

Luminal B tumours can be *PR* positive or negative. These cancers differ from luminal A in that there is higher expression of the proliferation protein, *Ki-67*, and in general, they are classified as higher grade than luminal A (Table 1.3). In addition, this subgroup can overexpress *HER2*. Consequently, this subgroup of breast cancers is often associated with a higher rate of recurrence than luminal A breast cancers (Creighton, 2012).

Table 1-3 Luminal subtypes classification from the WHO

| | ER | PR | HER2 | Ki-67 |
|------------------------------------|-----------|-----------------------|-----------------------------------------------------------|---------------------------------|
| Luminal A | Positive | Positive | Negative | Low |
| Luminal B HER2 negative | Positive | Low/Negative | Negative | High +/- PR negative and low |
| Luminal B HER2 positive | Positive | Positive/Low/Negative | Positive for overexpression and/or amplification | Any level |

Note: Luminal subtype classification modified from WHO Lokuhetty, D., White, V. A., Watanabe, R., & Cree, I. A. (2019). WHO Classification of Tumours Editorial Board. Breast Tumours. *WHO Classification of Tumours Series, 5th ed.; International Agency for Research on Cancer: Lyon, France, 2, 88-97.*

1.7.1.3 HER2 positive

Human Epidermal Growth Factor is overexpressed in 15-20% of all breast cancers (Rakha et al., 2023). These tumours tend to be associated with poorer prognosis, although with the evolution of *HER2* directed therapy, this may translate into an improvement in survival in these patients (Rakha et al., 2023). Gene expression assays are generally not indicated in these cases, as tumours that are *HER2* positive are treated with targeted treatment and chemotherapy, either in the adjuvant or neoadjuvant setting.

Overexpression of *HER2* is noted in 2-15% of lobular breast cancers and is more commonly associated with the high grade tumours (Cancer Genome Atlas Network, 2012; Christgen et al., 2019 Rakha et al., 2008). In the presence of *HER2* overexpression (positivity), adjuvant directed therapy, usually in combination with chemotherapy, is indicated, so, as stated above, genomic testing is not performed.

1.7.1.4 Basal-like

Basal-like tumours are a heterogenous group of cancers that typically do not express *ER*, *PR* or *HER2* (Rakha et al., 2009). These breast malignancies are often high-grade ductal cancers which, although generally chemosensitive, are often associated with reduced survival rates compared with the other subtypes (Rakha et al., 2009). As they do not express the hormonal receptors, adjuvant endocrine therapy is not normally indicated in these types of breast cancer.

1.7.2 Standard Prognostic Indicators

Historically, the main parameters used as prognostic tools in breast cancer have been tumour size, grade, lymph node status. The Nottingham Prognostic Index (NPI) was developed incorporating these features. NPI is widely used to assess prognosis and decide on adjuvant treatment, assigning cases into a prognostic category (Table 1.4). This, and the two online tools that are used in the UK, *Adjuvant! Online* and PREDICT, are outlined below.

1.7.3 Nottingham Prognostic Index

The NPI has been validated as a tool which can help provide prognostic information for an individual with breast cancer (Balslev et al., 1994; Blamey et al., 2010). In 1982, Haybittle and colleagues (1982) analysed data from 387 patients, performing multiregression analyses of recurrence and survival rates concluding that combining tumour grade, size and lymph node status improved prediction of outcomes following breast cancer surgery. In general, breast cancer is classified into one of three NPI categories (Galea et al., 1992. Gray et al., 2018; Haybittle et al., 1982). The predicted

prognosis decreases as the indices rise. The cut-offs used for each prognostic group are illustrated in Table 1.4.

Table 1-4 Nottingham Prognostic Index Categories

| Prognosis | Score |
|-----------|-------------|
| Good | ≤ 3.4 |
| Moderate | > 3.4 – 5.4 |
| Poor | > 5.4 |

Note: The prognosis is inversely related to the NPI score. The table illustrates the commonly used cut-off levels.

Despite the well-recognised importance of grade, size and lymph node status, a systematic review and meta-analysis of 19 studies (Gray et al., 2018), found that there were significant differences in the NPI and survival data. The evidence suggesting that both biological and molecular features influence tumour behaviour and prognosis, so the quest began for tests that reflect this heterogeneity, aiming for a more personalised approach to prognostication.

1.7.4 Online Prognostic Tools for Breast cancer

Prognostication in breast cancer can help guide decisions regarding adjuvant therapy following surgery for early breast cancer. Although these discussions often require a nuanced approach, the quantitative information that prognostic tools provide, can assist consultations surrounding the risks and benefits of treatment more empirically. The output of both tools is dependent on the accuracy of the clinicopathological assessment. In addition, the use of discrete categories in the size and nodal status can affect the sensitivity of the results.

Adjuvant! Online and PREDICT (see 1.8.4.1 & 1.8.4.2 below), are two clinically validated online prognostication tools that have been widely used in clinical settings nationally and internationally (Engelhardt et al., 2017). Only PREDICT includes the *Ki-67* and *HER2* status, and neither interface incorporates tumour *PR* status, limiting their overall utility and applicability. An additional point of note is that the reporting of *Ki-67* has yet to be incorporated into standard histology reporting in the UK (Jones et al., 2017). A multicentre study assessing the prognostication of breast cancer

patients using *Adjuvant! Online* and PREDICT, found that although both tools were generally satisfactory at predicting mortality, the variability of results in patients under 50 years of age highlighted the need to consider the risk of over or underestimation, especially in this age group (Engelhardt et al., 2017).

1.7.4.1 *Adjuvant! Online*

The *Adjuvant! Online* tool was created to help inform decisions regarding the benefit of adjuvant treatment following surgery for early breast cancer. This clinically validated online model was created in 1998 using Surveillance, Epidemiology and End Results (SEER) data from adjuvant therapy trials (Ravdin et al., 2001). Details entered include age, menopausal status, comorbidities, tumour size, lymph node and ER status. The programme produces estimates for prognosis, for the use of 5 years of Tamoxifen and, in addition, overall outcomes. The omission of important prognostic indicators such as *PR* and *HER2* status, and *Ki-67* level was a recognised limiting factor, such that chemotherapy benefit can be overestimated in some groups (Campbell et al., 2009; de Glas et al., 2014). It has been postulated that as the data used to model *Adjuvant! Online* was obtained from patients in the USA SEER database, it may not be directly applicable to patients treated in countries with differing survival rates (Campbell et al., 2009).

1.7.4.2 *PREDICT*

The prognostic algorithm, PREDICT, was developed in 2010 from the Cancer Registry database from the UK with the aim of estimating the benefits of adjuvant therapy in breast cancer (Wishart et al., 2010). The model incorporates patient characteristics such as age, tumour factors, such as mode of detection (screening or symptomatic), tumour size, grade, lymph node status and *ER*, *HER2* and *Ki-67*. It has been clinically validated (Engelhardt et al., 2017; Wishart et al., 2011) and is available as an online tool for clinicians. A recent update of the programme, Version 2, has demonstrated an improved prognostication for patients under 40 years of age (Candido Dos Reis et al., 2017). However, the programme references *Ki-67*, a molecular marker that has yet to be incorporated into standard pathology reporting of breast tumours in the UK (Jones et al., 2017). Although the tool can be used without this molecular marker, the authors

confirm that the inclusion of *Ki-67* has resulted in a statistically significant improvement in predicting outcomes for *ER* positive patients (Wishart et al., 2014).

1.7.5 Evolution of Genomic testing in Breast Cancer

Microarray gene technology has identified gene expression signatures in breast cancer that have enabled the development of prognostic and predictive tools. These are widely available and are used to tailor treatment in early luminal breast cancer. Although these commercially available tests have been validated in large studies with mixed tumour groups, the two tests that have been the most comprehensively evaluated in lobular cohorts are discussed in detail below.

1.7.5.1 Oncotype DX Breast Recurrence Score

Oncotype DX® RS (Genomic Health, Redwood City, CA) is a 21-gene genomic assay comprised of 16 reference and 5 control genes used in prediction and prognostication in hormone receptor positive breast cancer, which has been clinically validated as a prognostic and predictive tool in early breast cancer (Paik et al., 2004). The 16 reference genes include 5 proliferation related genes (*Ki-67*, *STK15*, *BIRC5*, *CCNB1*, *MYBL2*), 2 metastasis related genes (*MMP11*, *CTSL2*), 2 *HER2* related genes (*GRB7*, *HER2*) and 7 sex hormone related genes (*ER*, *PGR*, *BCL2*, *SCUBE2*, *GSTM1*, *BAG1*, *CD68*). The test result is produced as a Recurrence Score (RS), from which the risk of recurrence and the benefit of adjuvant chemotherapy can be predicted (Albain et al., 2010; Paik et al., 2006; Sparano et al., 2018). The RS ranges from 0 to 100, with patients categorised as low risk (<18), intermediate risk (18-25) and high risk (>25). Data from the TAILORX trial (Sparano et al, 2019), further categorised the levels by age differentiation, finding that women 50 years or younger had a 1.6% benefit with chemotherapy for RS 16-20, a 6.5% benefit for RS 21-25, and a substantial benefit for RS >25. Similar findings were also noted in the RxPONDER trial that analysed the impact of Oncotype DX® RS testing in early breast cancer, in the node positive setting (Kalinsky et al., 2021). This RS stratification has helped tailor treatment decisions in ductal tumours.

The evidence for genomic testing of lobular breast cancer in early breast cancer is less robust. Several trials have reviewed the data from larger studies, extracting outcomes for the patients with ILC as a secondary analysis. Other investigators have performed retrospective analyses on lobular cohorts with RS testing. Commonality within the studies was that most patients with ILC have a low or intermediate risk Oncotype DX® RS (Christgen et al., 2020; Conlon et al., 2015; Makower et al., 2022; Tadros et al., 2018; Tsai et al., 2016; Weiser et al., 2022), with higher RS typically, although not exclusively, found in patients with the pleomorphic subtypes of ILC (Felts et al., 2017). Interesting, a retrospective study in 2017 on SEER data of 7316 ILC specimens with Oncotype DX® RS testing, found 21% with low RS, 71% with intermediate score (11-25) and 8% with high scores (Kizy et al., 2017). This study also confirmed that high scores were not exclusive to the pleomorphic subtype, with some classic lobular cancers having a RS over 25. In addition, although lobular cancers are considered less chemosensitive than other breast tumours, some studies noted a benefit of adjuvant chemotherapy, in terms of DFS and OS, in certain patients with RS results greater than 25 (Weiser et al., 2022). Highlighting the fact that the genomic pattern of ILC differs from IDC, such that models incorporating these differences may provide better predication for the lobular cohort. LobSig is a newly developed gene signature which has been tailored to reflect lobular pathology with the potential to improve prognostication in this special type of breast cancer (McCart Reed et al., 2019; Oesterreich et al., 2022). The results of studies that provide evidence to validate this test are keenly awaited.

1.7.5.2 MammaPrint

MammaPrint was one of the first gene expression tools developed to assess the risk of recurrence in women with early breast cancer, using a 70-gene signature test to classify patients into high- or low-risk groups (van 't Veer et al., 2002). The MINDACT trial (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) was a multicentre, randomised clinical trial conducted to evaluate the clinical utility of MammaPrint in guiding decisions on adjuvant chemotherapy in women with early breast cancer (Cardoso et al., 2016). Genomic results and clinicopathological features of the cohort, assessed using *Adjuvant! Online*, were reviewed. Patients with low genomic risk and high clinical risk were randomised to

two groups, chemotherapy, or no chemotherapy. The results of the MINDACT trial found that the addition of MammaPrint to traditional clinical risk assessment identified a cohort of postmenopausal women with a high clinical risk and a low genomic risk, who can avoid chemotherapy without an increased risk of recurrence (Cardoso et al., 2016; Sparano et al., 2019). A recent update on the study performed with approximately nine years of follow-up, has confirmed the findings of the original investigation, demonstrating that women over 50 years of age with high clinical and low MammaPrint risk only derive a 2.6% benefit from adding chemotherapy to endocrine therapy (Piccart et al., 2021).

Although most of the research into the utility of MammaPrint has been performed with no differentiation of tumour groups, several studies have reviewed the evidence for lobular cohorts (Abel et al., 2021; Beumer et al., 2016; Jenkins et al., 2022; Metzger et al., 2020). Jenkins et al (2021), identified 2610 cases from the National Cancer Database (NCDB) in the USA with lobular cancer who had undergone MammaPrint testing. The primary aim of the study was to assess OS based on the genomic risk assessment, and in addition, to evaluate the benefit of adjuvant chemotherapy in the cohort with a high genomic score. The results found that patients with a high genomic risk score had worse survival rates, although the benefit of chemotherapy could not be satisfactorily predicted. The evidence for prognostication with MammaPrint was also found in the study by Beumer and colleagues (2016), especially in patients with node negative disease, although the proportion of ILC classified as low or intermediate risk was higher than the IDC cohort. Abel et al, (2021) evaluating the use of MammaPrint in 1,497 ILC cases from the NCDB also found that compared with IDC, ILC cases were more likely to have discordant genomic testing results. The level of discordance noted in the study in the high clinical and low genomic risk category was 76.1% v 51.7%, for lobular and ductal cases respectively ($p=0.026$), and this was particularly evident in under 50 age group (Abel et al., 2021). This study highlighted the need for further investigation into genomic testing specifically designed for lobular cohorts of patients.

1.7.5.3 Gene Expression Profiling Tests Evaluated in Lobular Cohorts

The introduction of the first two gene expression tests, Oncotype Dx and MammaPrint, into mainstream care in breast medicine was followed by second generation multigene

assays, some of which incorporate clinical variables to produce a risk stratification model. Several have been evaluated in retrospective studies comparing lobular and ductal outcomes. EndoPredict®, a 12 gene molecular assay, analyses the expression of eight cancer related genes (*BIRC5*, *UBE2C*, *DHCR7*, *RBBP8*, *IL6ST*, *AZGP1*, *MGP*, *STC2*), three reference genes and one control gene (Filipits et al., 2011). A prognostic prediction score (EPclin) is calculated from the EndoPredict® assay, tumour size and nodal status to produce a high or low risk score through a diagnostic algorithm (Dubsky et al., 2013). A study assessing the prognostic value of EPclin to predict distant recurrence at 10 years compared the outcome data of 470 patients with ILC and 1,944 patients with IDC. The analysis included cohorts from three large clinical trials with a minimum of nine years follow-up, (Sestak et al., 2020). The results found EPclin risk stratification in node negative early breast cancer provided significant prognostic value in both the IDC and ILC subtypes. Similar findings were also reported in a study reviewing the utility of EndoPredict® in 24 (18%) ILC and 121 (77.6%) IDC patients, where EPclin resulted in de-escalation of treatment in one third of patients (Almstedt et al; 2020).

Another prognostic test, Prosigna, developed from the Prediction Analysis of Microarray (PAM50), a 50 gene assay provides a risk of recurrence (ROR) score between 1 and 100 for disease relapse within 10 years. The test algorithm for ROR includes molecular subtype (luminal A, luminal B, *HER2* enriched or basal like) (Section 1.7.1), tumour size and proliferation score. Prosigna is used to predict the risk of recurrence for postmenopausal patients with *ER* positive, *HER2* negative breast cancer with less than four nodes involved and a tumour size under 5cm. Low scores suggest a low risk of recurrence and endocrine therapy is usually recommended, with chemotherapy advised for patients with a high score (Gnant et al., 2014). A retrospective population-based trial in Denmark assessed the ROR of 1570 patients (21.72% with ILC) with early breast cancer treated between 2000 to 2003 (Lænkholm et al., 2020). The study found that although the ROR provided significant prognostic information in both tumour types (IDC and ILC), poorer outcomes were noted for lobular patients in the same ROR score group. Similar findings were described in a recent multicentre study assessing the prognostic utility of another gene expression based signature, the Breast cancer Index (BCI) (Nunes et al., 2021). The prognostic ability of BCI was assessed using specimens from 376 patients with lobular breast

cancer. The authors concluded that BCI facilitated risk stratification in ILC, especially in the low risk groups where de-escalation of treatment could be considered (Nunes et al., 2021). Some authors in this study had investigated the use of the Genomic Grade Index (GGI) in a lobular cohort (Metzger-Filho et al., 2013). The GGI, a validated assay based on the expression of 97 mostly proliferative genes, is designed to objectively define histological grade assessment (Metzger Filho et al., 2011; Sotiriou et al., 2006). The researchers noted that in a lobular cohort, the GGI provided prognostic information that was independent of tumour size and nodal status (Metzger-Filho et al., 2013). However, median follow up in this study was 6.5 years which may not have captured late recurrences that can occur with ILC.

1.7.6 Systemic Inflammatory Indices

The role that inflammation plays in tumour development and progression is well recognised (DeNardo & Coussens, 2007; Jiang & Shapiro, 2014; McAllister & Weinberg, 2014). Systemic inflammatory markers assessed from peripheral blood samples have been evaluated as potential prognostic and predictive markers in malignancies (Faria et al., 2016; Paramanathan et al., 2014; Yang et al., 2018). These systematic reviews and meta-analyses suggest that the ratios derived from peripheral blood may have potential as prognostic markers in patients with cancer. It is worth noting that the large systematic review and meta-analysis by Paramanathan and colleagues, which evaluated 49 studies, incorporating 14, 282 patients, found that the variability of the reference ranges for NLR was significant. However, the results from this study demonstrated a strong association with poor prognosis when the ratio was over 5 (Paramanathan et al., 2014).

The use of systemic inflammatory tests had been explored in the early 20th century, by the team that proposed the use of the Glasgow Prognostic Score (GPS) (McMillan et al, 2007). This was one of the first tests developed which used markers of inflammation to evaluate prognosis in patients with cancer. The GPS is based on the level of C-reactive protein (CRP) and albumin, calculating a prognostic score, which has subsequently been modified (mGPS) to recognise that a low albumin was not clearly correlated with poor survival (McMillan et al, 2007). Findings from a systematic

review by one of the original researchers (McMillan, 2013), concluded that the GPS/mGPS is a reliable indicator of prognosis in patients with operable and advanced cancer (McMillan, 2013).

Following on from this seminal work, researchers looked to other markers such as the Neutrophil to Lymphocyte ratio (NLR), the Platelet-to Lymphocyte ratio (PLR), the Monocyte to Lymphocyte ratio (MLR) and the Systemic Inflammatory Index (SSI) to investigate potential in the prognostication of solid malignancies. Systematic reviews evaluating the prognostic value of inflammatory indices, especially the NLR, in studies on oesophageal, nasopharyngeal, biliary, pancreatic cancer and other solid malignancies found good correlation with outcome (Dolan et al., 2018; Yang et al., 2018). A recent meta-analysis reviewed the evidence for systemic inflammatory markers in primary breast cancer (Savioli et al., 2022). Of the 3310 studies identified, 42 were eligible for inclusion. Each of the indices was analysed separately. The studies were heterogenous regarding the cut-off levels set. However, the results suggested that elevated indices were associated with outcome, with raised preoperative NLR associated with poor prognosis (Savioli et al., 2022). These findings were also noted in two systematic reviews of 15 studies (Ethier et al., 2017), and 45 studies (Corbeau et al., 2020), assessing the use of NLR in breast cancer.

1.8 STUDY HYPOTHESIS AND AIMS

Lobular carcinoma of the breast is the second most common type of breast cancer accounting for 5-15% of all breast malignancies. ILC is more mammographically and sonographically occult when compared with the most common type of breast cancer, IDC. Tumour size and extent is often underestimated by mammography such that standard preoperative imaging protocol for ILC is Breast MRI for patients planned for conservative breast surgery.

DBT has been shown to increase cancer detection rates in studies both in the screening and symptomatic populations. A recent meta-analysis reviewing data from 17 screening studies, found that the combined incremental cancer detection rate was 1.6 cancers/1000 assessments when compared with 2D imaging (Marinovich et al, 2018). This improvement is partly due to the ability of tomosynthesis to highlight margin assessment by enhancing in-plane visibility as the technological advantages of DBT result in less glandular tissue overlay. In addition, mammographic features which are often associated with ILC, such as architectural distortion (Chamming's et al, 2017), are more evident with tomosynthesis, such that the preoperative size assessment of ILC may be improved in a selection of patients.

DBT was introduced into the three specialist breast units within the HDUHB from 2010. The system was first used in Prince Philip Hospital and rolled out to the other two sites in 2013. In 2013, the system upgrade included the addition of C-view (s2D) software, in each of the three hospitals within the NHS Trust utilising Tomosynthesis in the assessment of symptomatic breast patients. The hypothesis of the first section of the thesis is that DBT in combination with s2D will reduce the need for breast MR in the preoperative assessment in a selection of patients with ILC.

The second analysis investigates the potential utility of the NPI, the Oncotype DX® RS and 4 systemic inflammatory indices that have been evaluated in solid tumour studies in early breast cancer, as recent systematic reviews suggest that these indices may help in the decisions regarding adjuvant therapy. The hypothesis of the second component of the thesis is that a correlation exists between the RS, NPI and SII in selected clinical cases, such that the use of the Oncotype DX® RS testing maybe triaged toward moderate and high risks groups based on the inflammatory indices.

1.9 AIMS AND STUDY PLAN

1.9.1 Preoperative Imaging Aims

The primary aim is to review, interpret and calculate the size of ILC using DBT/s2D and breast MRI tumour measurements in a cohort of patients diagnosed between 2013 and 2021 and to compare the results with the final pathology measurement, to identify whether the introduction of DBT has improved the preoperative size assessment in this tumour group.

1.9.1.1 Secondary Aims

1. To compare and contrast the preoperative assessment of ILC using Breast MRI versus DBT/s2D to ascertain whether there are any subgroups of patients in whom the addition of MRI may not improve surgical outcomes.
2. Review the mammographic imaging findings to assess whether any specific descriptor or breast density is associated with poor correlation with final pathology.
3. To evaluate the use of sonography in the preoperative assessment of ILC comparing the results with the other imaging modalities investigated.

1.9.2 Systemic Inflammatory Indices Aims

The aim of the study is to review the Oncotype DX® RS results of women treated for node negative, early breast cancer and assess correlation with the systemic inflammatory indices calculated from the preoperative blood, and the NPI calculated from the final histology results. In addition, the study will investigate whether these predictive and prognostic abilities vary depending on breast cancer type. The lobular cohort results for Oncotype DX® RS, NPI, systemic inflammatory indices, and clinicopathological features will be evaluated separately.

To assess correlation between the Oncotype DX® RS and NLR, PLR, MLR, and SSI.

1. To evaluate whether there is greater correlation with certain pathological groups.
2. To utilise the information to potentially develop a simple, inexpensive predictive and prognostic tool for patients with hormone receptor positive early Invasive Lobular carcinoma of the breast.

CHAPTER 2: GENERAL MATERIALS AND METHODS

This chapter documents the methodological approach, research design and statistical analysis selected for both parts of the study. The first section describes the preoperative imaging assessment of ILC of the breast comparing MRI and DBT. The second section evaluates the use of the systemic inflammatory indices NLR, PLR, MLR, and SII as possible predictive and prognostic indicators in early breast cancer, assessing any potential correlation with Oncotype DX® RS and/or NPI.

Ethical and Institutional board approval was obtained for the two studies: IRAS reference numbers 18/NI/0025 for the imaging section and 20/LO/0850 for the systemic inflammatory indices study. Patient consent was not required given the study design. Engagement with breast cancer patient groups was undertaken to inform these decisions.

2.1 ILC PREOPERATIVE IMAGING STUDY

2.1.1 Study Design

Studies looking specifically at ILC tumour size are mostly retrospective in nature and frequently performed in a combined screening and symptomatic setting. This is in part due to the low incidence of ILC (7-15%) when compared with the more prevalent type of breast cancer IDC NST (60-75%) and balanced with the need for an adequate sample size for validity and statistical significance. Prospective designs are more suited to a screening population, often multicentre in design, evaluating imaging assessment of an ILC cohort with DBT as a secondary analysis. In these trials, the cancer detection rates were generally low, ranging from 0.56 - 0.94% (Zuckerman et al., 2020). This is explained by the relatively lower incidence of ILC (7-15%), such that the CDR of ILC would be 0.0392 – 0.141, thereby requiring a large sample size to find any statistical significance.

A prospective paired-study design was initially considered, with MRI imaging of all patients with a confirmed cancer of the breast. As resources were not available for this,

a proof of principle concept retrospective two-reader pilot study was designed to compare the preoperative size assessment of ILC, comparing DBT/s2D with Breast MRI, with final pathology size as the gold standard. The study design was created with the potential to inform a power calculation to plan a future prospective study.

2.1.2 Sample Population

The Hywel Dda University Health Board (HDUHB) Breast department in Prince Philip Hospital (PPH) covers a wide geographical area in Southwest Wales with a population of over 400,000. The demographics, characteristics, and population figures overall are relatively constant, although the latest figures from the Office for National Statistics (2023) indicate a steady increase in the proportion of the ageing population in Wales.

The unit has referrals from Primary and Secondary care and accepts cases diagnosed at the Breast Test Wales (BTW) screening unit in Swansea. On average, 4000 new symptomatic patients are seen each year. There are over 450 breast cancers treated in HDUHB per annum. All cancer diagnoses in Wales are currently registered on the Cancer Network Information System Cymru (CANISC). Search of the database identified individuals with a diagnosis of ILC from 2013 to 2021. A total of 400 female patients with ILC were recorded on CANISC, with an age range of 37 to 92 years. Subjects who had received definitive primary surgery were considered for inclusion. Patients with mixed ductal-lobular breast cancer were excluded, as these are not recognised as pure ILC in the WHO classification (Metzger-Filho et al., 2019). Review of the patient records identified individuals who had received treatment with neoadjuvant/Primary endocrine therapy or chemotherapy, and these were also excluded. At the start of the study in 2018, 74 patients were eligible for inclusion, after excluding cases without complete imaging (10), the final cohort was 64. The study continued to recruit until 2021, with ILC cases identified in the MDT meeting post-surgery. All cases were rechecked for eligibility and assigned a trial number. In total, 103 patients were recruited into the study. As stated in 2.1.1, the sample size in this retrospective analysis was primarily determined by the relatively low incidence of ILC. The cohort size, however, is consistent with that seen in the literature.

2.1.3 Pathology Data Collection

Histology reports for the cohort were reviewed on the pathology database and cross-checked to confirm ILC morphology and inclusion eligibility. The data collection tool in Appendix D was completed. Details recorded on the proforma included: size of the cancer (in mm) and any additional invasive foci, presence of any intraductal component (LCIS/DCIS), axillary lymph node status and hormone receptor/HER-2 receptor status. Operative details were noted including type of breast surgery; mastectomy or conservative surgery (wide local excision or oncoplastic conservative surgery). Management of the axilla was recorded, with the number of sentinel/axillary nodes removed, including the number of any involved lymph nodes. If further surgery was required, any additional histology, malignant or benign, was added to the form.

2.1.4 DBT Image Protocol

DBT was introduced into symptomatic assessment in PPH in 2010. BTW commenced DM screening in 2013, with additional tomosynthesis imaging for recall and preoperative assessment. Tomosynthesis was introduced into the other two breast sites in the HDUHB in 2013.

2.1.4.1 Tomosynthesis Equipment

DBT mammography is performed with Selenia Dimensions System (Hologic, Bedford, MA, USA) in screening and symptomatic assessment. Standard imaging generally involves 15 low-dose projections for each view (4 views per patient). The images are displayed on a dedicated Hologic SecurView DX workstation optimised for both 2D and 3D imaging.

The DBT mammograms were independently viewed and reported by the two readers (author and AM) using standard reading protocols, consistent with current clinical practice with 4 images displayed (2CC and 2MLO), followed by the 2 CC and then the 2 MLO views for each patient.

2.1.4.2 Tomosynthesis Image Retrieval

Images from screening and PPH were downloaded from the PACS system. All images were anonymised and linked to the patient ID number by an independent mammographer (HW), who created reading lists for review in dedicated viewing sessions.

2.1.4.3 Inter-reader Concordance

Prior to reporting, the readers met to discuss lesion measurement with DBT. Following routine clinical practice, size was assessed in the longest plane in millimetres. A retrospective reader study was performed to investigate measurement variability and to inform the study on interobserver variation. The readers reviewed tumour measurements from the image database of the previous 20 cancers reported by both the author and Dr Moalla, Consultant Radiologist, Prince Philip Hospital, HDUHB (AM). Cohen's Kappa coefficient to assess inter-reader concordance suggested that there was agreement within 5mm.

As there is some debate in the medical literature around the use of Cohen's Kappa coefficient regarding the influence of sample size and validity (McHugh, 2012; Zhao et al,), the intraclass correlation coefficient (ICC) was calculated to measure the reliability in the measurements of the size of the tumours and the density of mammograms, as observed by the two observers (Reader1 and Reader 2), with an ICC value less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.9 suggesting poor, moderate, good, and excellent reliability, respectively (Koo & Li., 2016).

2.1.4.4 Data Collection Tool: Imaging

Database collection proforma for DBT, MRI and Sonography were created by the author and agreed by the two readers (author and AM). Both readers have over 25 years of breast imaging reporting experience. The proformas can be viewed in the Appendices. Following the first independent reporting session, the readers met to discuss the DBT form design and measurement protocol. As lesion measurement was not possible using synthetic images for all cases, it was agreed that s2D/C-view measurements would be excluded in the subsequent reading rounds. The DBT data

collection form (A) was subsequently modified to reflect the working practice of the radiology team.

2.1.4.5 DBT Reporting

The readers (AM) (1) & author (2) independently reported in separate reading sessions. The anonymised DBT images were viewed on dedicated workstations as 1mm reconstructed slices, with reference to the s2D (C-view) images if needed. Real time adjustment, magnification and windowing was permitted, reflecting normal working practice. Tumour size was assessed on both tomosynthesis views (MLO & CC) in the slice/frame that demonstrated the lesion most clearly and measured in millimetres in the longest plane with the online screen ruler. As spiculae are generally regarded as a desmoplastic reaction (Flanagan et al, 1996), if this finding was present, the main mass was measured and the spiculae were not included in the size measurement, as per standard practice.

The site of any lesion, the radiographic abnormality, including the extent and presence of any microcalcification, and breast density were recorded on the Mammogram Imaging Data collection form A (see Appendix 1.1). If no lesion was seen or measurement was not possible, the abbreviation NR was recorded.

2.1.5 MRI Image Protocol

MRI Breast is performed on a 1.5T (GE Healthcare Signa HDxt, Waukesha, WI) with the patient in the prone position using a dedicated breast coil. Prior to the procedure a canula is placed in the cubital vein for administration of gadolinium intravenous contrast. MRI Sequences are performed Axial T1 FSE Asset, Axial T2 FSC Ideal, Axial DWI ASSAET, followed by Axial VIBRANT Multiphase MPH with gadolinium contrast. Contrast is given during the last sequence for the contrast uptake curve.

2.1.5.1 MRI Measurement Protocol

A dedicated breast radiologist (Reader 1, AM) with over 20 years of Breast MRI experience, reported the imaging findings in real-time with review of the mammogram. This reflects normal working practice, thereby ensuring no impact on patient care. The images and data were retrieved and reviewed for accurate data collection. The maximum diameter of the lesion was measured in millimetres in the longest plane. The site, and description of all abnormalities was noted and recorded on the data collection form B (Appendix 1.2).

2.1.6 Breast Ultrasound

Breast Sonography is performed in all symptomatic cases on General Electric (GE) Logiq E9 Ultrasound machine with a ML5-16-D wideband matrix linear array 15MHz probe. In screening, breast ultrasound is performed on GE Logiq E7, and GE Logiq E9 with high-resolution probe 13.5 MHz or 15 MHz probe. Sonography is a dynamic investigation with real-time measurement performed. In both symptomatic and screening assessments, lesion size is measured in the longest plane (mm), the image descriptor is included, as per standard radiological reporting (Appendix 1.3).

2.1.6.1 Sonographic Measurements

83 Ultrasound images were retrieved from Picture Archiving and Communication System (PACS). Missing images included 10/103 (9.71%) from the symptomatic cohort and 10/103(9.71%) from screening. The images were anonymised into a worklist by HW. The reports were reviewed and image measurements with descriptors were recorded (data collection sheet B) for each patient.

2.1.7 Data Analysis Preoperative Imaging Study

Statistical analysis was performed using IBM SPSS software version 28.0.1.1 (4) operating in a Windows environment, with support from Dr Mike Kiernan. Primary Pathology, DBT, MRI, measurements and US data distributions were assessed for

normality using the Shapiro-Wilk test. Pearson’s and Spearman’s correlation tests were used to test for correlation for normally distributed and or non-gaussian (skewed) data respectively. The strength of Spearman’s correlation coefficient were used in the analysis and shown in Table 2.1 (Mukaka., 2012).

Table 2-1 Strength of the correlation for Spearman's Rank Correlation Coefficient for value of Rs

| The strength of a correlation | |
|------------------------------------------------------------------|---------------------------|
| Value of coefficient <i>R_s</i> (positive or negative) | Meaning |
| 0.00 – 0.19 | A very weak correlation |
| 0.20 – 0.39 | A weak correlation |
| 0.40 – 0.69 | A moderate correlation |
| 0.70 to 0.89 | A strong correlation |
| 0.90 to 1.00 | A very strong correlation |

Note: Ramsey, P. H. (1989). Critical Values for Spearman’s Rank Order Correlation. *Journal of Educational Statistics*, 14, 245 - 253.

Analysis of imaging and pathology was performed for each reader for all imaging modalities. Correlation coefficients for imaging were calculated for each reader.

Reliability analysis was assessed between the two readers using percent agreement and weighted kappa statistics. Inter reader reliability was measured using Pearson’s linear correlation coefficient R for both readers and calculated for each modality, with intraclass correlation between the two readers. Intraclass Correlation Analysis was calculated for the whole cohort, and then repeated after excluding outliers. These calculations could have been affected by data variability. Standard working practice in HDUHB is to accept the general measurement agreed by the two readers.

The statistical analysis was repeated for each modality assessing imaging sizes within +/- 5mm tolerance. This reflected clinical practice when deciding whether an individual patient can be considered for conservative breast surgery. These calculations were compared between the two readers and for each imaging modality.

The effect of breast density on reader interpretation was investigated for the three imaging modalities, comparing average density with average DBT, sonography and MRI, measurements with tolerance +/- 5mm. Multiple linear regression testing was performed as a final analysis, with the assistance of Dr Mike Kiernan.

2.2 DATA COLLECTION SYSTEMIC INFLAMMATORY INDICES

2.2.1 Introduction

All patients diagnosed with node negative early breast cancer between 2013 and 2020 were identified on the CANISC database. Sample size was based on inclusion criteria, rather than on sample size calculations, with individuals who had received Oncotype DX® RS testing being considered for inclusion in the study.

The Oncotype DX® RS database was reviewed and completed by accessing the paper records and the online portal on Exact Sciences Inc (formerly known as Genomic Health Inc.). The clinical, pathological and outcome data for the cohort were recorded. Operative details including the axillary nodal status were entered into the database. Patient demographics were recorded. Family history, comorbidities, medication history, and smoking history were also noted. All samples were matched and anonymized before use.

Ethical approval required the submission of a statistical protocol written by Dr Gareth Davies. The need for informed consent was waived by the IRAS committee.

2.2.2 Sample Population

A single centre retrospective cohort analysis was undertaken comparing various indices and scores for a patient population from a single Health Board, in Southwest Wales. As such, there was no control group, no blinding, and no randomisation.

All patients with IDC or ILC who had Oncotype DX® RS performed in the adjuvant setting in early breast cancer in HDUHB were considered for inclusion. Other WHO recognised tumour subtypes were omitted from the cohort. Exclusions included patients that had been lost to follow up, and cases where no preoperative blood results were recorded. Patients with preoperative blood tests taken within two weeks of the surgical procedure were considered for inclusion.

The HDUHB has three district general hospitals within the trust performing breast surgery. The surgical oncology team introduced Oncotype DX® RS testing for

selected patients with node negative early breast cancer in 2007. The decision to offer testing at this time was made at the MDT meeting. Clinical and pathological factors were considered along with the NPI. Following NICE guidance in 2018, patients assessed as being at intermediate risk of recurrence using the NPI, are eligible for Oncotype DX® RS testing (National Institute for Health and Care Excellence (NICE), 2018).

Recurrence score (RS) results are held on the Hywel Dda University Health Board Surgical Oncology Database and can be accessed on the online Exact Science portal (formerly Genomic Health). Oncotype DX® RS testing is performed on unstained slides of formalin-fixed paraffin-embedded tissue as per the manufacturer's guidelines.

2.2.3 Oncotype DX® RS Results and Categorisation

Paper results of all patients from HDUHB who received Oncotype DX® RS testing for early breast cancer from 2007 to 2017 were retrieved from file. From 2017, the reports were held on a secure database. Patient names were collected, anonymised and given a unique ID. For individuals in the database with missing RS, the online reports were accessed on the Exact Science website (formerly Genomic Health), via a secure unique portal.

Patients with results of post-surgical RS testing between 2007 and 2021 were identified and given unique identification numbers. Some of these patients had been included in a decision impact and economic evaluation study in Southwest Wales (Holt et al., 2013). In total, 602 patients were identified.

Exclusion criteria included: Oncotype DX® RS for preinvasive histology (DCIS), pure tubular, mucinous or medullary histology and presence of axillary node positivity. Mixed ductal/lobular histology or ductal with mucinous features were included in the ductal cohort. All patients included in the study were female.

A final analysis dataset was created after exclusions and anonymized.

2.2.4 Data Collection Health Records

Data retrieved from patient records included age at diagnosis, date of diagnosis, comorbidities, past medical history, smoking status, medication at time of diagnosis, family history (including BRCA status if known), date last seen (follow-up period), dates and types of recurrence if any, date of death and cause of death. Subjects lost to follow-up were excluded from the study.

2.2.5 Peripheral Blood Calculation

The preoperative Full Blood Count (FBC) was used to calculate the NLR, MLR, PLR and SII for each patient in the cohort. The SII was calculated using the formula Neutrophil Count x Platelet count/Lymphocyte count (N x P/L). The cut-off levels were chosen following review of the literature. Recent Caucasian population-based prospective cohort studies suggested reference levels for the inflammatory markers, where a 97.5% limit of normal was used as a cut-off between normal and elevated: NLR = 3.53, PLR = 246, MLR = 0.47, SII = 1169 (Fest et al, 2018. Forget et al, 2017). Patients with no preoperative peripheral blood analysis were excluded from the study.

2.2.6 Pathology Database

Pathology reports for the cohort were retrieved. Operative details with date of procedure noted. Tumour characteristics recorded included size, grade, axillary lymph node status, presence of DCIS or LCIS, hormone receptor status (ER and PR levels).

The NPI was calculated for all patients using the formula: $NPI = \text{tumour size in cm} \times 0.2 + \text{Tumour Grade (1-3)} + \text{lymph node status (1=negative, 2=1-3 nodes positive, 3 = >4 nodes positive)}$. The groups were classified into the 3 categories (consistent with the literature): Good < 3.4, Moderate > 3.4 – 5.4, Poor > 5.4 (Gray et al, 2018).

2.2.7 Data Analysis

Analysis was conducted in Stata/IC v16 operating in a Windows environment, with Dr Gareth Davies and Professor Paul Lewis providing statistical assistance and support, in accordance with the conditions of ethical approval from IRAS. The database was analysed to assess correlation between the NPI, Oncotype DX® RS and the inflammatory indices calculated for each individual patient. Survival outcome, using Kaplan-Meier survival analysis, was performed to look at each prognostic indicator without adjustment, using published cut points where available.

Statistical correlation models were employed to investigate the correlation between the RS, NPI and systemic inflammatory indices. The dataset was analysed with both tumour subtypes, ILC and IDC and, also investigated separately to evaluate the effect of tumour subtype on Oncotype DX® RS and outcomes.

After exclusions, the cohort consisted of 495 patients. The dataset was analysed as a whole and then separated by age, in keeping with clinical practice, investigating correlation in the over and under 50 age group. Subgroup analysis was performed by breast cancer type, with the two main histological groups, ductal and lobular, analysed separately with adjustments made for covariates during multivariable analyses.

RS levels were grouped into two categories, high and low risk, with high risk > 25 in patients over 50, and >18 in under 50 years of age, as these were the standard cut-offs for consideration of chemotherapy benefit in Southwest Wales at the time of the study.

CHAPTER 3:IMAGING ASSESSMENT ILC

3.1 INTRODUCTION

Accurate preoperative staging is important in the management of the newly diagnosed patient with breast cancer for treatment planning. Tumour size prediction is required to inform decisions on the most appropriate operative intervention and in addition, in certain situations, to direct management towards neoadjuvant therapy such as chemotherapy or primary endocrine treatment to downstage the tumour. Large prospective trials including all breast cancer subtypes have shown that preoperative tumour size assessment is improved with DBT when compared with DM and US, as lesion conspicuity is enhanced by the reduction of glandular tissue overlap such that margins are highlighted with this technology (Chamming's et al., 2017. Destounis et al., 2013. Förnvik et al., 2010. Girometti et al., 2018. Luparia et al., 2013. Mariscotti et al., 2016. Michell & Batohi., 2018. Mun et al., 2013. Seo et al., 2014. Timberg et al., 2010). Most studies report a significant improvement in assessment (>60%) when compared with standard 2D imaging, with higher specificity noted on tomosynthesis in all ages and breast density groups (Conant, et al, 2019. Heywang-Köbrunner et al, 2022. Luparia, et al, 2013).

Many studies in the symptomatic setting have assessed the utility of DBT for screening recalls, reimaging equivocal cases with tomosynthesis to evaluate diagnostic accuracy. As tomosynthesis reduces superimposition, recalls for indeterminate asymmetry can be triaged more easily, resulting in downgrading or upgrading of the findings, thereby reducing recall rates. In addition, DBT imaging has improved both the definition of masses (Hofvind et al., 2018. Raghu et al., 2016), and detection of architectural distortion (Dibble et al., 2018; Mariscotti et al., 2016), an imaging feature that can be missed on standard mammography. One study found that 55% of distortions seen on tomosynthesis were occult on DM (Freer et al., 2014).

There are fewer studies in the symptomatic clinic setting and, in general, most have been conducted without differentiation of tumour groups. Early research into the use of tomosynthesis evaluated the use of the technology as an additional imaging tool to standard 2D mammography, concluding that DBT significantly enhanced diagnostic

performance, as indeterminate lesions were often downgraded (Bansal & Young, 2015; Choudhery et al., 2021).

The importance of imaging patients with breast cancer is in the initial detection of the lesion and then to guide the biopsy of any abnormality, and finally for assessment for surgery. Management decisions around surgery rely on accurate tumour size measurement and detection of multifocality. Tomosynthesis has been shown to improve these assessment categories in studies which did not differentiate between tumour groups (Mariscotti et al., 2016; Michell & Batohi., 2018).

As breast imaging with sonography often underestimates tumour size (Gruber et al., 2013), and MRI has been shown to increase mastectomy rates due to overestimation of disease extent (Bleicher et al., 2009; Houssami et al., 2008; Sardanelli et al., 2022), the use of tomosynthesis may result in an improvement in the preoperative size assessment in some categories of patients, such that imaging with MRI in ILC can potentially be omitted in some clinical scenarios.

3.1.1 Mammographic Size Assessment of ILC

Mammography is universally accepted as the main imaging modality in breast screening and assessment. In general, size assessment of breast tumours on imaging is challenged by several issues, namely, anatomical noise (Cederström & Fredenberg., 2014; Kavuri & Das., 2020.), the growth pattern of the malignancy and the presence of extensive calcifications, the latter reducing the accuracy of preoperative evaluation on mammography whilst having less effect on tumour measurement assessment with MRI (Weiss, et al., 2014). Key developments in imaging technology have improved preoperative assessment, however there are recognised problems with respect to lobular breast cancers.

Traditionally, ILC has been shown to be difficult to detect on standard breast imaging as mammographic findings can be variable (Muttalib et al., 2014). Although lobular cancers can appear as a spiculated mass on mammography, there may only be a subtle distortion of the surrounding breast tissue, or an asymmetrical density, calcifications or rarely ILC can present as a soft tissue density (Chamming's et al., 2017; Johnson et

al., 2015; Lopez and Bassett., 2009) (Section 1.5.1). In addition, lobular tumours are more often occult on standard imaging than other breast subtypes (Michael et al., 2008), and have a greater propensity to be multifocal, multicentric and bilateral, compounding the complexity of the preoperative assessment (Quan et al., 2003). These features can partly be explained by the distinctive growth pattern of ILC which can cause difficulties with both detection and measurement. As the lobular tumour cells invade, there is minimal desmoplastic reaction which results in less disruption of the surrounding breast architecture. This feature of lobular cancer is due to the loss of E-cadherin, a protein involved in cell adhesion (Pramod et al., 2021) (Section 1.2 & 1.2.2).

Many of the older studies reported variable mammographic sensitivities to ILC ranging from 35 to 83% (Berg et al, 2004; Mandelson et al., 2000; Michael et al, 2008; Weaver et al, 2020), findings consistent with a recent review of the literature, which also concluded that the presence of dense breast tissue reduced sensitivity to less than 11% (Weaver et al., 2020). The results of many of these studies may be limited by the mammographic technology of the time. A subanalysis of a large multicentre trial conducted in a screening population comparing standard 2D imaging to DBT, found that the sensitivity for ILC detection increased from 0.27 to 0.55 per 1000 screens with the use of tomosynthesis (Friedewald et al., 2014). This statistically significant increase in sensitivity for detection of ILC was also noted in a study investigating the utility of DBT in the preoperative staging of patients with dense breast tissue when compared with digital mammography (Krammer et al., 2017).

Although studies have consistently shown that tomosynthesis has increased cancer detection rates, with higher sensitivity and specificity, compared with standard 2D imaging, there is less evidence regarding the effect of DBT on the assessment of ILC. Studies evaluating ILC tumour size on DBT have mainly been performed in the symptomatic sector, with screening studies evaluating the technology in this group of patients as a secondary analysis (Table 3.1). The sample size in these former trials is limited by the relatively low incidence of ILC, with many having sample sizes of less than 100. Marinovich et al (2018), in a systematic review of studies assessing tumour size by DBT and other imaging found 8 studies that met their inclusion criteria. The research was conducted between 2009 and 2016. Of the articles included, there were

5 full text articles and 3 conference abstracts. The studies were heterogenous, often including all tumour types, with modest sample sizes. In addition, prototype DBT machines were used in two of the experiments. The review concluded that both over and underestimation occurs in tumour size assessment with DBT, and although tomosynthesis improved evaluation in dense breasts when compared with standard 2D mammography, the variability in measurement was such that there was a risk of incorrectly staging the patient (Marinovich et al., 2018).

Table 3-1: Studies Assessing Size of ILC with Digital Breast Tomosynthesis in Screening and Symptomatic Populations.

| PUBLICATIONS | Sample Size ILC/n | Correlation Coefficient DBT with Pathology | DBT concordance with Pathology | Correlation Coefficient MRI with Pathology |
|---------------------------------|-------------------|--------------------------------------------|--------------------------------|--------------------------------------------|
| Förnvik et al, 2010* | 14/73 | 0.86 $p=.035$ (all tumour types) | | |
| Wall et al, 2011 θ | 23 | 0.73 | | 0.86 |
| Luparia et al, 2013 | 31/149 | 0.86 | 66.4% DBT | 70.5% |
| Seo et al, 2013* | 3/84 | 0.9 all densities 0.87 dense breasts | | |
| Marsicotti et al, 2014 | 40/200 | | | |
| Mariscotti et al, 2016 | 83 | | | 0.81 |
| Chamming's et al, 2017 | 20/43 | 0.24 intraclass coefficient | | |
| Förnvik et al, 2018 \dagger | 6/103 | 0.73 | 57.8% | |
| Girometti et al, 2018 \square | 7/74 | 0.39 to 0.62 intraclass coefficient | | 0.81 to 0.85 |
| Selvi et al, 2018 | 85/155 | | Overestimation 5% | Overestimation 26% |
| Garlaschi et al, 2019 | 14/105 | 0.24 | 28.57% | |

Note: Studies assessing preoperative size assessment of ILC with DBT. Some studies were subanalyses with marked heterogeneity. * Prototype machine used; \dagger Dense breast population; θ Conference article; \square 4 reader study and mixed Ductolobular cancers analysed.

In general, studies suggest that the detection and assessment of all breast cancers has been improved with DBT. As the technology reduces the effect of anatomical noise and tissue overlap, a limiting factor in imaging lobular cancers, this may translate into improved preoperative tumour measurement. In addition, algorithms enhancing the visualisation of microcalcification has also added to the increase in cancer detection rates seen with tomosynthesis (Choi et al., 2016). It is useful to explore how

technological advancement in these three components, anatomical noise, growth pattern and calcification, has contributed to breast screening and assessment.

3.1.1.1 Anatomical Noise

Anatomical noise refers to the effect that normal anatomy creates in a radiological image. In breast imaging with mammography, contrast between fibroglandular and adipose tissue can result in anatomical noise. This may obscure the object of interest and has been shown to have a greater effect on the detection of certain mammographic abnormalities than quantum noise (Cederström & Fredenberg., 2014). This is of particular importance in patients with dense breast tissue, such that tumour size assessment is often underestimated (Van Goethem et al., 2004).

Studies have shown that the introduction of tomosynthesis has reduced structural noise in mammography, such that tumour margins are more conspicuous, and the effect of tissue overlap is reduced (Sechopoulos & Ghetti., 2009). This has improved cancer detection in density categories B & C, however, there is still a lack of evidence to suggest that DBT has improved imaging in very dense breast tissue (Category D), (Conant et al., 2019; Rafferty et al., 2016). Although developments in tomosynthesis algorithms have resulted in lesion enhancement in dense tissue, only contrast enhanced spectral mammography (CESM) has been shown to significantly reduce the effect of anatomical noise resulting in an improvement in assessment for all tumour subtypes (Hill et al., 2013; Lobbes et al., 2023).

3.1.1.2 Growth Pattern

Most lobular cancers of the breast are characterised by the loss of E-cadherin, an adhesion molecule located on chromosome *CDH1* gene (McCart Reed et al., 2015; Pramod et al., 2021). The lack of E-cadherin results in the tumour appearing as small discohesive cells that infiltrate the stroma in a diffuse single-file pattern resulting in limited disruption of the surrounding tissue. Mammographically, this lack of desmoplastic reaction can result in the tumours being occult on imaging, especially in dense breast tissue (Mariscotti et al., 2016). This partly explains why lobular cancers are disproportionality represented in cohorts of missed cancers in screening (Gilliland et al., 2000; Porter et al., 1999). Tomosynthesis has the potential to enhance the detection of ILC as it reduces superimposition such that subtle changes in the

parenchyma may be more evident. Studies suggest that the detection of lobular cancer has been improved, however the evidence for improvement in staging with DBT is still variable.

3.1.1.3 Calcifications

The detection and assessment of calcifications in the breast is an important aspect of screening and symptomatic mammography. The presence of calcifications may indicate signs of invasive or pre-invasive breast cancer. Mammographic calcification associated with ILC, although not common, can be seen especially in the presence of DCIS and LCIS (Geogian-Smith & Lawton., 2001; Venkitaraman., 2010). Several studies found that ILC is associated with calcification in 0 to 28% of cases (Butler et al., 1999; Krecke & Gisfold., 1993; Tagliati et al., 2021). Although initially it was felt that this may be an underestimation in the older studies as the technology at this time was SFM. Current available evidence also suggests that it is not common to see calcification associated with lobular carcinoma in the absence of DCIS or LCIS. A recent retrospective study assessing the use of CAD in the detection of ILC in 153 cases, noted only 22.22% of cases without an in-situ component were associated with microcalcifications (Arce et al., 2023).

Initial studies evaluating the detection and assessment of calcifications on DBT suggested that tomosynthesis was inferior to digital mammography (Kopans, et al., 2011; Tagliafico, et al., 2015). However, research conducted after these earlier studies show that with the improvements in algorithms that enhance calcification visualisation, coupled with the introduction of computer generated synthetic digital images, tomosynthesis with s2D has now been shown to have similar detection rates to digital mammography (Choi et al., 2016; Destounis et al., 2013).

3.1.2 Sonographic Size Assessment ILC

Breast ultrasound is an imaging tool that is used extensively across the world as an adjunct to standard mammography in assessment and diagnosis. Review of the literature suggests that sensitivities for the detection of ILC on sonography are between 68% and 98%, with the higher values noted in the more recent studies, a probable

consequence of the improvement in the technology and transducer frequency from 7.5MHz to 13.5 and 15MHz (Butler et al., 1999; Chapellier et al., 2000; Dillon et al., 2006; Evans & Lyons., 2000; Munot et al., 2002; Paramagul et al., 1995; Pointon & Cunningham.,1999; Porter et al, 2014., Selinko et al., 2004; Skaane & Skjorten., 1999).

Size assessment of breast tumours with ultrasound demonstrates relatively high sensitivity in the evaluation of well defined rounded masses, especially when the lesion is under 20mm (Luparia et al., 2013; Vijayaraghavan et al., 2018). However, ILC typically does not have a distinctive appearance on sonography and is most often seen as an irregular hypoechoic ill-defined mass which is associated with posterior acoustic shadowing (Chamming's et al., 2017; Lopez & Bassett., 2009; Selinko et al., 2004) (Section 1.5.2). One study assessing the imaging of ILC with ultrasound in 20 women, concluded that in 31.8% of ILC cases, the sonographic abnormality appeared as a vague distortion of the tissue with posterior acoustic shadowing (Ferré et al., 2017). These distortions are difficult to measure owing to the lack of margin demarcation, such that accurate assessment of these lesions is challenging with ultrasound often underestimating tumour size in up to 53% of cases, by a mean 3.5mm (2-8mm) (Gruber et al., 2013; Ozcan et al., 2023; Vijayaraghavan et al., 2018; Wong et al., 2018), with the degree of underestimation increasing with mass size (Wong et al., 2018). In addition, the pathological size discrepancy noted with sonography can be increased in the presence of an extensive intraductal component (Gruber et al., 2013; Luparia et al., 2013).

3.1.3 Magnetic Resonance Imaging Size Assessment ILC

MRI of the breast provides high resolution imaging with kinetic enhancement of the tissue, a feature often associated with cancer (Kuhl., 2007; Mann et al., 2008; Mann et al., 2019). These kinetic curves are viewed following the administration of intravenous (i.v.) gadolinium contrast agent. These curves are generally classified into three types. Type I describes a gradual rise in signal intensity over time which is usually associated with benign pathology. Type II curves are seen where the initial steady increase which is followed by plateauing in the later stages. This feature is suspicious of malignancy. A Type III curve is seen where there is a rapid increase in enhancement which is then

followed by a reduction in the enhancement toward the end of the study, a feature consistent with malignancy (Kuhl., 2007; Mann et al., 2019).

Pooled sensitivity and specificity rates of 93% and 71% respectively for breast cancer detection are noted in the literature (Neeter et al., 2023). However, the use of MRI in staging a newly diagnosed breast cancer has been thoroughly investigated, and as studies have failed to show a survival benefit in cases where MRI detected more extensive disease (Turnbull et al., 2010), the investigation is now employed for specific indications. In the UK, one indication for breast MRI is in the preoperative assessment of patients with ILC who are planned for conservative breast surgery. Studies have shown that MRI has a higher sensitivity rate for both the detection and assessment of lobular cancer than the current standard imaging modalities, sonography and mammography, with sensitivity rates quoted in the literature greater than 95% (Brennan et al, 2017. Hovis et al, 2021. Mann et al, 2008. Wong et al, 2018). The main benefits of performing preoperative MRI screening in patients with ILC is in the assessment of lesion size and, additionally, in the detection of multifocality and synchronous contralateral disease which are mammographically occult. Studies consistently demonstrate detection rates of additional disease foci in up to 30% in patients with ILC (Bansal et al., 2016; Mann et al., 2008; Mann, 2010), with a third of these lesions found to be benign on biopsy (false positives) (Brennan et al., 2009; Houssami et al., 2008; Plana et al, 2012). This can result in delays in treatment while the findings on MRI are reviewed with second look ultrasound, and, for additional biopsy results. The consequence of which, often results in an increase in mastectomy rates for this subtype of breast cancer (Mann et al., 2008). Additionally, as noted in Section 1.5.3, there is some debate surrounding the incidence of contralateral disease in lobular cancer, with one UK study comparing outcomes in over 38,000 women, where 14.15% of the cohort had ILC, concluded that there was no significant difference in the incidence of bilateral disease in the two histology groups (Langlands et al., 2016). The authors proposed the idea that the use of preoperative MRI should be restricted to patients undergoing breast conservative surgery (Langlands et al., 2016). However, a more recent retrospective analysis performed in the USA, noted contralateral disease on MRI in 3% of the ILC cases, suggesting that preoperative MRI should be considered in all patients with ILC (Cocco et al., 2021).

Preoperative size estimation on MRI demonstrates overall good correlation with final pathological size of all breast cancer types (Boetes et al., 2004; Ozcan et al., 2023; Rominger et al., 2016). Studies in the literature assessing the extent of the lobular cancer, however, indicate that underestimation of tumour size with MRI, is found in approximately 59.1%, with overestimation seen in 36.7% (Boetes et al., 2004; Gruber et al., 2013; Hovis et al., 2021; Mann et al., 2010; Muttalib et al., 2014; Parvaiz et al., 2016; Selvi et al., 2018). One study investigating the factors that may predispose to imaging discrepancy between the pathological size of ILC and MRI assessment, concluded that accuracy decreases with larger cancers and, also, in the presence of diffuse in-situ disease, with MRI overestimating tumour size (Gest et al., 2020).

Breast density is known to significantly increase the risk of breast cancer (Bodewes et al., 2022; Boyd et al., 2007; Engmann et al., 2017; Ginsburg et al., 2008; Pettersson et al., 2014; Vacek & Geller, 2004). In addition, the sensitivity and specificity of mammography is reduced in dense breast tissue, such that supplemental screening with MRI is employed for this specific indication in some countries (Melnikow et al., 2016). However, the evidence for the use of MRI in dense breast tissue is mixed, with some studies finding that the rate of false positives requiring biopsy after MRI is higher in dense breast tissue, with no benefit in long term outcomes (Elmi et al., 2021; Seely et al., 2016).

3.2 AIMS & OBJECTIVES

The main aim of this study was to evaluate the accuracy of DBT and MRI in the preoperative size assessment of tumour extent in patients with lobular cancer. Subgroup analysis, to investigate the effect of breast density on measurements, was also performed. Secondary analysis of the utility of sonography in size assessment of ILC was evaluated in this cohort of patients.

Statistical analysis of the findings to calculate correlation with final pathology was performed, comparing the results with MRI to ascertain whether tomosynthesis improves tumour size estimation. The database was reanalysed to assess the effect of breast density, and, in addition, with a tolerance of 5mm, reflecting clinical practice.

Finally, multiple linear regression models were applied to the database to assess which of the imaging modalities provided the most precise lobular tumour measurements. The covariates, breast density and age, were included in the modelling. Only patients with all imaging modality measurements were included in the analysis. The two extreme outliers were excluded from the analysis.

3.3 MATERIALS AND METHODS

3.3.1 Cohort Recruitment

The number of patients diagnosed with primary invasive lobular breast cancer in HDUHB between 2013 and 2021 were identified from the CANISC database. Part of the data collection occurred during the COVID19 pandemic, which increased the number of patients prescribed primary (neoadjuvant) endocrine therapy (n=56). Neoadjuvant therapy is given to reduce preoperative tumour size. Patients who had received chemotherapy or endocrine therapy prior to definitive surgery were excluded from the study, as this would have affected final pathology size. Additionally, during the pandemic, patients often opted for a mastectomy rather than conservative breast surgery. Anecdotally, patients did not want to risk having a second operation for involved margins, and, also, did not want to travel for adjuvant radiotherapy which resulted in a reduction in cases with MRI imaging.

The dataset was crosschecked with the Hywel Dda NHS University Health Board pathology records for each subject to confirm eligibility, with exclusions if the pathology was mixed ductal-lobular, rather than pure lobular carcinoma. Subjects who did not have preoperative DBT and/or MRI imaging were also excluded from the study. The final cohort size was 103 (Figure 3.1), a sample which is in keeping with the literature from studies in symptomatic clinics.

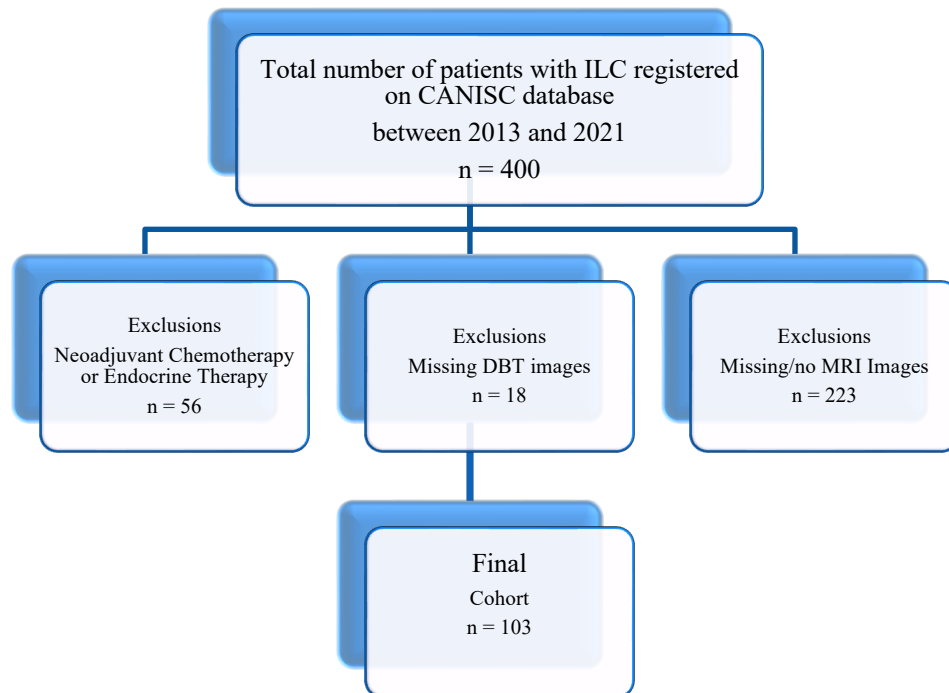


Figure 3.1 Lobular imaging study cohort

Note: ILC cohort of patients included in study from 2013 to 2021 from HDUHB

3.3.2 DBT Imaging Reporting

Images for the cohort were retrieved and anonymised. Worklists were created, as described in Section 2.1.4. The two readers independently reported the imaging findings in separate sessions. Data collection sheet A was completed independently by Reader 1 and 2. Each lesion was measured and assigned an imaging category abnormality. The presence of calcification was noted. As stated in Section 2.1.4, C-view measurements were discontinued as these were not being utilised clinically as stand-alone images.

The mammographic descriptors mirrored those used in daily practice. The films were analysed and reported with findings entered onto the reporting form. The presence of a mass was noted, and whether it was rounded or spiculated. If the mammographic abnormality was a distortion or an asymmetrical density this was noted, along with the presence of calcifications (Table 3.2). If more than one image feature was noted, this was also reported.

Table 3-2 Image Descriptor on Data Collection Sheet DBT

| MAMMOGRAPHIC ABNORMALITY |
|---------------------------------|
| N = NONE/NORMAL |
| SM = SPICULATED MASS |
| M = WELL DEFINED MASS |
| AD = ARCHITECTURAL DISTORTION |
| AS = ASYMMETRY |
| MC = MICROCALCIFICATION |

Breast density was defined subjectively until 2015 when the Hologic Tomosynthesis equipment in HDUHB was upgraded to include Quantra breast volumetric assessment. Reader 1 and 2 reported breast density for each study subject (Table 3.3).

Table 3-3 BI-RADS Breast Density Classification

| Breast Density | BI-RADS CLASSIFICATION |
|----------------|-----------------------------------------------------------------------------|
| A | The breasts are almost entirely fatty |
| B | There are scattered areas of fibro-glandular tissue |
| C | The breasts are heterogeneously dense, which may obscure small masses |
| D | The breasts are extremely dense which lowers the sensitivity of mammography |

Note: Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Service Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Jan. (Evidence Syntheses, No. 126.) Table 1, BI-RADS Breast Density Descriptions. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK343794/table/ch1.t1/>

3.3.3 Sonography Assessment

Images from the cohort were retrieved and anonymised as per section 2.1.6. As sonography is real-time imaging, tumour measurements and descriptors were obtained from the images and reports on the PACS system. A significant number of the cohort had missing ultrasound images which could not be retrieved. This reduced the cohort with sonographic measurements to 83.

3.3.4 MRI Assessment

Breast MRI is performed in HDUHB by a single radiologist reporting in real-time. The investigation is interpreted with knowledge of the DBT findings, as per normal clinical

practice. The images and reports were retrieved and anonymised. The data of lesion measurements and imaging findings were collected from the reports, as described in Section 2.1.5.

3.3.5 Pathology Database

Surgical histology results for the cohort were reviewed on CANISC and crosschecked with the pathology database on Welsh Clinical Portal (WCP). Demographic details were recorded in addition to operation details, year of diagnosis, Grade of ILC, invasive tumour size (any additional foci noted), presence of an in-situ component (DCIS/LCIS), lymph node status, receptor status, and any additional findings (Appendix D).

3.3.6 Database Analysis

The database was analysed using IBM SPSS 28.0.1.1 (14). As the data were not normally distributed, median values, interquartile range, and 95% confidence levels were presented for each imaging category. Wilcoxon Signed Rank tests were applied to evaluate any difference between the 3 imaging methods and final pathology. Spearman's rank correlation coefficient was calculated to examine the relationship between the imaging modalities and final pathology. Separate analyses were performed on the database to assess the effect of breast density. The effect of tumour size was evaluated by analysing the level of agreement for T1 lesions (less than 20mm), and T2 and T3 groups. Additionally, the imaging data were reanalysed with size tolerances of +/- 5mm.

Further analysis was performed using multiple linear regression modelling, with the assistance of Dr Mike Kiernan, to evaluate the size assessment obtained with DBT, USS and MRI, to investigate which imaging tool provided the most accurate size measurement when compared with final pathology. Cases with missing values from any of the imaging modalities were excluded (n=25). Additionally, extreme outliers

were removed from the dataset for the multiple linear regression analysis (Leys et al., 2019).

MINITAB software was utilised to construct the graphs and charts. This visual analysis was conducted to summarize the main characteristics of the data collected in the image study. A matrix plot was constructed to visualise the multivariate linear relationships between the final pathology estimates of the tumour sizes, the pre-operative tumour sizes estimated by DBT (Reader 1 and Reader 2), MRI, and USS. Error bar charts were constructed to visually compare the mean sizes \pm 95% confidence intervals (CI) of the tumours, estimated by three imaging modalities and the final pathology sizes. The mean \pm 95% CI of the differences between the final pathology sizes of the tumours and the sizes estimated with the three imaging modalities were also compared. If the 95% CI of the mean tumour sizes estimated using the different imaging modalities and final pathology did not overlap, then the tumour size estimates were assumed to be mutually exclusive and clinically significant. Scatter plots of the measures of tumour size and the covariates were examined visually to test the underlying assumption of linearity between the size measurements, the years of age of the patients, and the two categories of tumour density (Category 1 = low; Category 2 = high).

3.4 RESULTS

3.4.1 Cohort Characteristics

The number of patients who received primary surgery for ILC within the study period was 241. All patients were female and Caucasian, with an age range of 37 to 82, mean age 61.9 years. Most of the cohort were over 50 years of age (91.26%). All the patients under 50 were from the symptomatic group, comprising 8.74% of this imaging cohort.

The overall ratio of symptomatic to screened patients was 56:47, with some variation depending on the year assessed (Table 3.4) This is partly explained by the change in practice in the screening population, as tomosynthesis has been routinely performed on all patients recalled for assessment from 2015. This was not standard practice at the start of this study (2013). Additionally, tomosynthesis was introduced into the other sites in Hywel Dda UHB in 2014, which also influenced the sample size (Table 3.4).

Although cases were included from 2013 to 2021, there was a peak in recruitment in 2019, as patients with ILC were proactively identified during the multidisciplinary team meetings. It is worth noting, that during the pandemic patients were often prescribed primary endocrine therapy thereby reducing the number of lobular cases. This is described in more detail in Section 2.1.2

Table 3-4: Cohort Characteristics

| Variable | n/N % |
|-------------------------------------------------------------|----------------------------------------------------------|
| Mean age, years (range) | 61.9 (32 – 83) |
| Symptomatic/Screening Ratio (percentage) | 56:47 (54.37%; 45.63%) |
| Imaging | Total n (%) |
| Mammographic Breast Density Category | |
| Category A - Almost entirely fatty, <25% fibroglandular | 3 (0.03) |
| Category B - Scattered fibroglandular tissue, 25 -50% | 65 (63.11) |
| Category C - Heterogeneously dense fibroglandular 50-75% | 31 (30.10) |
| Category D - Extremely dense fibroglandular tissue, >75% | 4 (3.89) |
| Imaging Abnormality on DBT (some with >1 feature) | |
| Spiculated Mass | 26 |
| Mass | 47 |
| Architectural Distortion | 34 |
| Asymmetry | 1 |
| Association with Calcification | 11 |
| Calcification without a Mass | 5 |
| Occult | 2 |
| Mean Size on DBT 1: 2 (range) | Reader 1: 21.27 (8 – 56) Reader 2: 21.47 (5 – 46) |
| Imaging Findings on Sonography (percentage of total) | |
| Mass | 69 (66.99) |
| Distortion | 33 (32.04) |
| Occult | 1 (0.01) |
| No Size Assessment | 16 (15.53) |
| Mean Size on Sonography in mm (range) | 15.1 (4.5 – 35.4) |
| Imaging Findings on MRI | |
| Unifocal Mass | 80 (77.67%) |
| Multifocality | 22 (21.36%) |
| Occult | 1 (0.97%) |
| Mean Size on MRI (range) | 27.7 (5.5 – 80) |
| Operative Intervention | |
| Conservative Breast Surgery | Total cohort: 58/103 (56.31%) |
| Screening | 33/47 (70.21%) of screening cohort |
| Symptomatic | 29/56 (51.79%) of symptomatic cohort |
| Mastectomy: | Total cohort = 45/103 = 43.69%, |
| Screening | 14/47 (29.79%) |
| Symptomatic | 27/56 (48.21%) |
| Final Histopathology | |
| Mean Size on Histopathology mm (range) | 27.1 (4 – 113.0) |
| Histopathology Tumour Stage: | n = 103 (1 case = no viable tumour after biopsy) |
| T1 | 37 (35.92%) (Screening 24; Symptomatic 13) |
| T2 | 59 (57.28%) (Screening 20; Symptomatic 39) |
| T3 | 7 (6.8%) (Screening 3; Symptomatic 4) |

| | |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tumour Grade on Final Histology: | n = 103 |
| I | 0 |
| II | 101 |
| III | 2 |
| Presence of in-situ component: | n = 103 |
| LCIS | 3 |
| DCIS | 7 |
| Hormone Receptor Status | |
| Oestrogen Receptor Positive (Allred Score ≥ 3) | 102 (99.03%) |
| Oestrogen Receptor Negative (Allred Score < 3) | 1 (0.97%) |
| Progesterone Receptor Positive | 85 (82.52%) |
| Progesterone Receptor Negative | 18 (17.48%) |
| HER2 status | |
| Negative | 100 |
| Positive | 3 |
| Nottingham Prognostic Index (%) | Range 3 to 5.1 |
| Good: ≤ 3.4 | 40 (38.83) |
| Moderate: $> 3.4 - 5.4$ | 61 (59.22) |
| Poor: > 5.4 | 2 (0.02) |
| Oncotype DX® RS | 33/103 of cohort RS |
| RS 0-10: | 3 |
| 10-18 | 16 |
| 18-25 | 13 |
| > 25 | 1 |
| Systemic Inflammatory Indices mean (range) n=103 | |
| NLR | 2.7 (1-16.2) |
| MLR | 0.2 (0.1-1.2) |
| PLR | 146 (58.3 – 730.0) |
| SII | 745.6 (219.1-7081.0) |
| Miscellaneous | |
| Deaths: n = 7 | Pure Bone Metastases: n = 2 Bone & Liver metastases: n = 1 Other malignancies: Bladder x 1, Melanoma x 1 Non cancer deaths: Cholangitis (1), Pulmonary Embolus (1) |
| Family History: n=9 | BRCA 2 Carriers; n=2 Strong Family history with no mutation identified in 6 panel testing n = 7 |

Note: Imaging assessment and outcomes of total cohort n=103

3.4.1.1 Surgical Management of Cohort

The protocol for preoperative assessment of ILC in patients planned for conservative breast surgery is breast MRI. Consequently, all subjects included in the study were planned for this procedure. The addition of MRI changed the surgical management from conservative breast surgery to mastectomy in 41.75% of the total study group. The change in surgical management was greater in the symptomatic group. The mastectomy rate for the symptomatic cohort was 48.21%, and for the screened cohort 29.79% (Table 3.4: Figure 3.2).

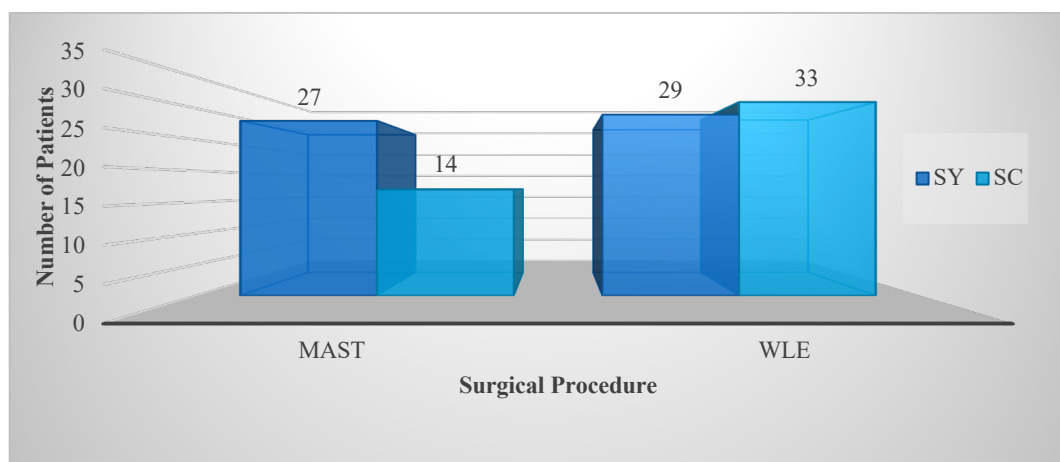


Figure 3.2 Surgical Procedure by Population

Note: Operative outcomes of the cohort (n=103) are shown for the two populations: Mastectomy (MAST) and conservative breast surgery (WLE). Symptomatic (SY n=56) cases; Screening cases (SC n=47).

As screened detected tumours are generally smaller than cancers diagnosed in symptomatic clinics, these results suggest that as the screening cohort lesions were smaller (Table 3.4), the mastectomy rate was also lower in this group (29.79%), with almost 50% of the symptomatic group undergoing a mastectomy, compared with 32.56% of the screened patients. The population demographics in Southwest Wales may also have accounted for the relatively high rate of mastectomies. As previously mentioned, geographically, a number of these patients live long distances from hospital, often in farming communities. The distance to travel for re-excision or a mastectomy for involved margins, with or without radiotherapy, may influence the patient choice of initial operation.

Assessing the effect of MRI on the management of patients under the age of 50 (n=9), demonstrates how the surgical outcome of this group was changed to mastectomy in seven of the patients (77.78%) (Figure 3.3). All the patients in this group were from the symptomatic cohort. This is understandable, as in general, breast screening starts at 50 years of age.

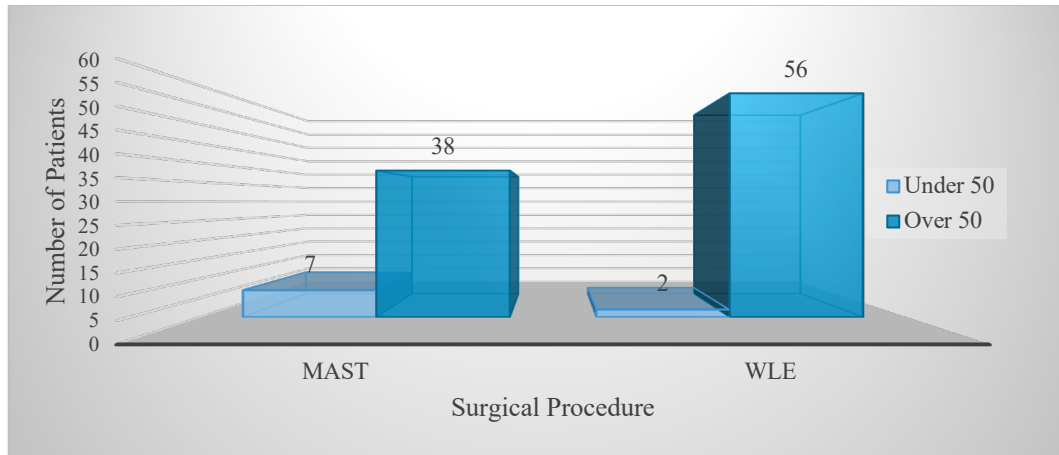


Figure 3.3 Surgical outcomes by age.

Note: 7 of the 9 patients under 50 years of age planned for conservative breast surgery (WLE) underwent mastectomy (MAST)

The mean tumour size in this age group was 41.33mm, compared with the mean tumour size on final pathology of the whole cohort 27.1mm. Three of the pathology cases were T3 (tumour sizes; 80, 71, 70). Interestingly, one patient with a low body mass index was diagnosed preoperatively by vacuum-assisted biopsy which removed the tumour in its entirety: final pathology measuring zero mm. The histology in this case demonstrated widespread LCIS with no residual invasive lobular cancer, which potentially affected the imaging pathology discordance on MRI. Additionally, this was an image detected area of microcalcification with no measurable disease on tomosynthesis and no abnormality seen on sonography.

Reviewing the data for the symptomatic and screening population, confirms how tumour stage is lower in the screen detected cohort of patients (Figure 3.4). This is an expected finding as screening aims to detect smaller tumours. Despite this, there were still 3 patients in the screening cohort with T3 cancers (tumour size greater than 50mm). These cases presented with multifocal lobular cancer: 55mm, 55mm and 63mm. The four T3 tumours in the symptomatic group were larger, with tumour sizes

113mm, 68mm, 70mm, 72mm. Two of these cases are significant outliers in the dataset as a large component of the multifocal lobular breast cancer in these cases was occult on MRI and tomosynthesis imaging.

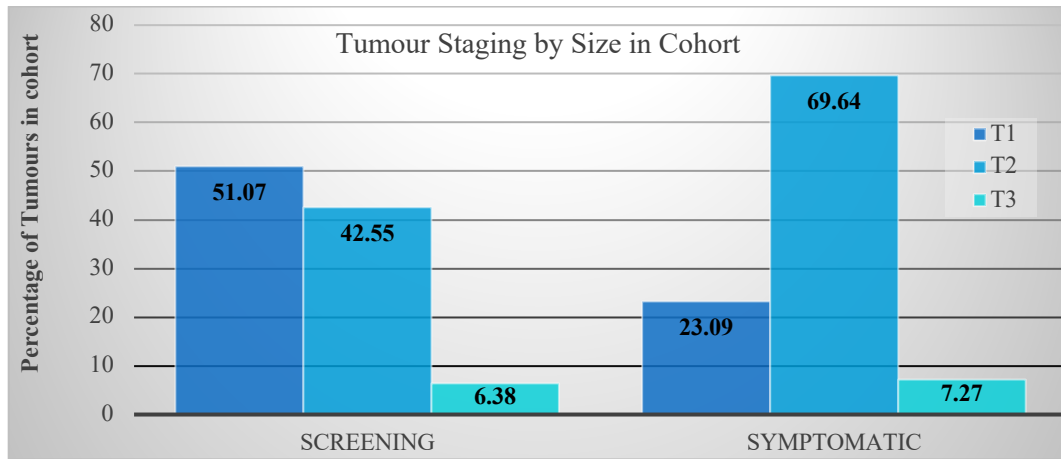


Figure 3.4 Tumour staging by size in screening and symptomatic cohort.

Note: Percentage of ILC according to tumour stage in screening (n=47) and symptomatic (n=56) cohorts. T1 tumour size < 20mm, T2 tumour size 20mm to 50mm, T3 tumour size >50mm.

Figure 3.4 clearly shows the effect of screening on tumour size, with 51% (24/47) of the cohort with T1, 42.55% (20/47) T2, and 6.38% (3/47) T3. In contrast, over two-third of the cases in the symptomatic setting are Tumour Stage T2 (69.94% n=39/56). Review of the dataset confirms that three of the T3 cases were under 50 years of age. However, the median age of patients with T3 tumours was 55 years (range 49 to 72).

3.4.2 Statistical Analysis

The database was analysed to evaluate which preoperative imaging modality, applied to a target population of patients with newly diagnosed lobular breast cancer, provided the most accurate and precise measurement of tumour size compared with the gold standard final histology size. The covariates considered were age and breast density.

Breast density was grouped into two categories, with the low breast density (Density A and B) Group 1, and the high breast density group 2 (Density C and D). This is consistent with clinical practice. The cohort consisted of 3 patients in Density A plus 64 in Density B (Category 1, n=67), and 32 in Density C plus 4 Density D (Category 2, n=36).

The level of agreement between Reader 1 and 2 of tumour size measurement and mammographic density was assessed by computing intraclass correlation coefficient (ICC). In this study with sample size of 103 (>52), for 2 observers, the point estimate ICC=.867 (95% CI between 0.790 and 0.926), suggested good reliability between Reader1 and Reader 2 (Table 3.5).

Table 3-5 Intraclass Correlation Coefficient for DBT Measurements

| Measures | ICC | 95% CI | | Hypothesis Test | | | |
|----------|------|--------|-------|-----------------|-----|-----|-------|
| | | Lower | Upper | F | df1 | df2 | P |
| Average | .867 | .790 | .926 | 7.53 | 74 | 74 | <.001 |

Note: The intraclass correlation coefficient (ICC) for tomosynthesis tumour size measurements between Reader1 and Reader 2.

The results were analysed as paired data for each reader for tomosynthesis, and single reader for MRI and breast sonography. Histograms were created to show the empirical frequency of the data (these are not included). Visual inspection suggested the pathology, tomosynthesis, MRI, and sonographic datasets was not normally distributed. This was confirmed by Shapiro-Wilk testing (Table 3.6).

Table 3-6 Shapiro-Wilk Testing for Normality

| Modality | Statistic | Significance |
|----------------------|-----------|--------------|
| Final Pathology Size | .861 | $p < .0001$ |
| DBT 1 Size | .935 | $p < .0001$ |
| DBT 2 SIZE | .977 | $p = .089$ |
| DBT Average | .973 | $p = .043$ |
| USS | .951 | $p = .003$ |
| MRI | .880 | $p < .0001$ |

As transformation of the data using natural logarithms was only partially successful, nonparametric analysis was conducted on the untransformed data. Wilcoxon Signed Rank tests were performed with all imaging categories to see whether the median distribution of the dataset on DBT, sonography or MRI, differed significantly with pathology. Spearman's Rank Correlation Coefficient was applied to the dataset to evaluate any agreement between the 3 imaging modalities and final pathology, applying the levels for correlation (Table 3.7).

Table 3-7: Strength of the correlation for Spearman's Rank Correlation Coefficient for value of Rs

| The strength of a correlation | |
|------------------------------------------------|---------------------------|
| Value of coefficient Rs (positive or negative) | Meaning |
| 0.00 – 0.19 | A very weak correlation |
| 0.20 – 0.39 | A weak correlation |
| 0.40 – 0.69 | A moderate correlation |
| 0.70 to 0.89 | A strong correlation |
| 0.90 to 1.00 | A very strong correlation |

Note: Ramsey, P. H. (1989). Critical Values for Spearman's Rank Order Correlation. *Journal of Educational Statistics, 14*, 245 - 253.

Descriptive data of tumour measurements on the final pathology, and on all the imaging modalities were analysed (Table 3.8). The mean and median tumour size on pathology were overestimated by MRI, and underestimated by both DBT and sonography, with the latter significantly underestimating the final histological size.

Table 3-8 Descriptive analysis dataset for imaging modalities (mm)

| | Pathology Size n=103 | DBT Reader 1 n = 96 | DBT Reader 2 n=97 | Combined DBT n=96 | Ultrasound n=83 | MRI n=103 |
|-----------------------------------------------------------|----------------------------|---------------------------|-------------------------|-------------------------|--------------------|-----------------|
| Mean | 26.89 | 21.56 | 21.87 | 21.72 | 15.08 | 27.58 |
| Range (min-max) | 0 – 113.0 | 8.0-56.0 | 6.9 – 46.0 | 7.45 – 45.50 | 4.5 – 35.4 | 5.5 – 80.0 |
| 95%CI for Mean Lower Bound - Upper Bound | 23.48-30.30 | 19.63-23.49 | 20.22-23.53 | 20.08-23.35 | 13.68-16.48 | 24.46-30.7 |
| Median | 22.50 | 20.50 | 21.750 | 21.00 | 14.20 | 23.00 |
| Interquartile Range | 20 | 10.0 | 12.0 | 11.25 | 8 | 17.0 |
| Skewness (Std.Error) | 1.923 (.246) | 1.007 (.246) | .439 (.246) | .550 (.246) | .862 (.264) | 1.356 (.240) |
| Kurtosis (Std. Error) | 6.476 (.488) | 1.336 (.488) | -1.46 (.488) | .016 (.488) | .887 (.523) | 1.724 (.476) |

Note: SPSS Descriptive analysis output for the cohort dataset for all measurements.

Review of the results in Table 3.8, illustrates how median tumour size differs significantly between final pathology and sonography: 22.5mm and 14.20mm, with the latter underestimating lesion size.

The MRI, Pathology and DBT Reader 1 measurements were highly skewed, with combined reader and sonography tumour size assessments being moderately skewed. Reader 2 data and pathology size skewness was less skewed. The kurtosis levels for all measurements reflects the significant outliers in the dataset. These measurements are included in this analysis as they represent true readings of the subjects in the cohort.

3.4.2.1 Pathology

Of the 103 patients, the pathology of one case (trial no. 24) had no residual invasive lobular cancer in the final histological specimen as the tumour had been removed during the preoperative vacuum-assisted diagnostic biopsy. The case was included in the analysis to avoid bias. Median tumour size of the cohort was 22.50 mm with an Interquartile Range of 20mm, with tumour sizes ranging from 0mm to 113mm (Table 3.9 & 3.10).

Table 3-9: Pathology size of cohort (mm)

| FINAL PATHOLOGY SIZE | Valid n= 103 |
|----------------------|--------------|
| | Missing n=1 |
| Mean | 27.530 |
| Median | 23.000 |
| Std. Deviation | 17.6628 |
| Range | 109.0 |
| Minimum | 4.0 |
| Maximum | 113.0 |

3.4.2.2 Digital Breast Tomosynthesis Results

The dataset for the 2 readers was analysed separately, and then averaged for evaluation. Wilcoxon Signed Ranks test confirmed that the DBT measurements for each reader (1&2) and for the averaged readings, differed significantly from the final pathology tumour size (Table 3.10),

Table 3-10: Wilcoxon Signed Ranks Test for Reader 1 & 2

| | Final Pathology Size DBT Reader 1 | Final Pathology Size DBT Reader 2 | Final Pathology Size DBT Average |
|-------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|
| Z | -2.688 ^a | -2.706 ^a | -2.733 ^a |
| Asymp. Sig. (2-tailed) | .007 | .007 | .006 |
| a. Based on negative ranks. | | | |
| b. Wilcoxon Signed Ranks Test | | | |

Note: Wilcoxon Signed Rank Test for both readers demonstrating that the size on tomosynthesis differs from final pathology $p=0.007$

3.4.2.2.1 DBT Tumour Size and Final Pathology

As previously stated, as the dataset was not normally distributed, non-parametric testing was applied.

Outliers significantly affected the distribution of the data (Table 3.9). As stated above, in the final analysis outliers were excluded, and the database was reanalysed using multiple linear regression modelling (Section 3.4.2.5). Plotting DBT average size with the final pathology size highlights these outliers (Figure 3.5).

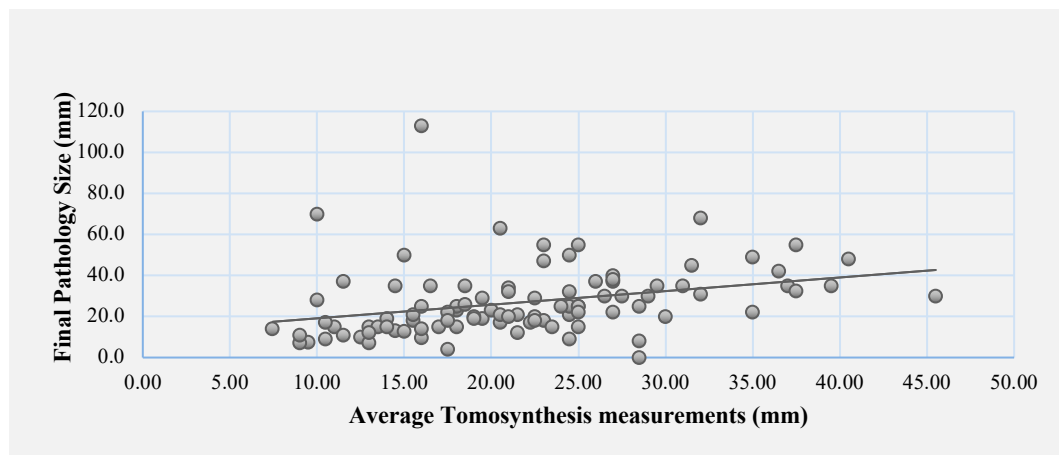


Figure 3.5 Average DBT measurements compared with final pathology.

Note: Spearman's rho correlation coefficient $r(94)=[.487]$, $[p=.000]$

The two most extreme outliers were both from the symptomatic sector. The pathological specimens confirmed a high burden of disease, with over 80mm of ILC in the final histology specimen:

- **Cohort no. 98:** A 70 year old lady who presented with a breast lump. Tomosynthesis demonstrated a vague area of distortion that was difficult to evaluate. Size estimation was 10mm and 22mm for reader 1 and 2,

respectively. The final histological size of the ILC component was 113mm and this case is seen as one of the outliers in Table 3.9.

- **Cohort no 103:** is also seen as an outlier with DBT sizes of 20 and 22mm for Reader 1 & 2 respectively. The final histological size was 76mm.

The histology of these cases did not contain any in-situ disease. Review of the imaging confirmed that the imaging measurements for all modalities were real. The discrepancy between the readers was related to the difficulty in assessing the margins of the subtle distortions seen on tomosynthesis in both patients.

Plotting the difference in sizes of DBT measurements with final pathology illustrates that tomosynthesis tends to underestimate tumour size, especially with large tumours. This is seen for both readers (Figures 3.6 & 3.7). Of note, Reader 1 reported size on 96 cases, finding no clear size for the remaining 7 patients. Reader 2 recorded 97 tomosynthesis measurements.

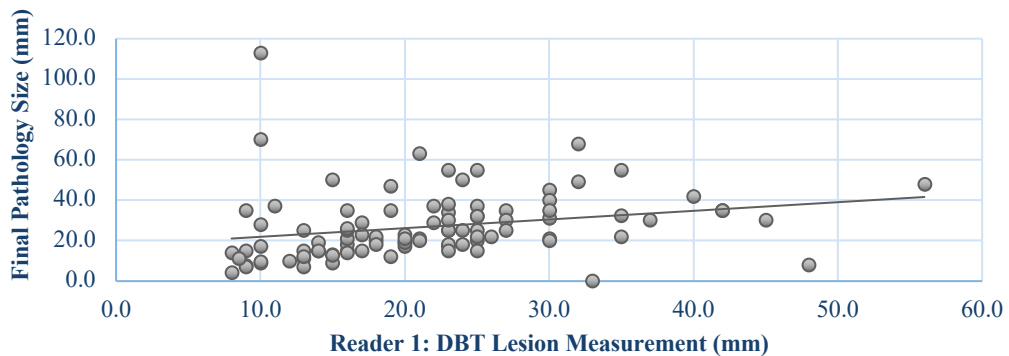


Figure 3.6 Reader 1 DBT measurements compared with final pathology.

Note: Spearman's rank correlation $r_s(94) = [.455]$, $[p.000]$.

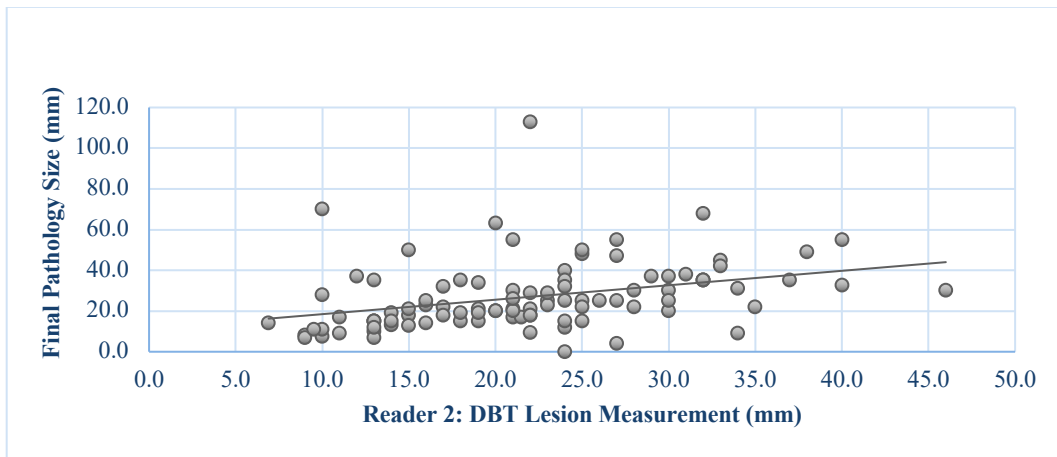


Figure 3.7 Reader 2 DBT measurements compared with final pathology.
 Note: Spearman's rank correlation $rs(95) = [.492]$, $[p=.017]$

Figures 3.6 and 3.7 demonstrate how tomosynthesis tumour measurements for both readers have some positive correlation with lesion size on pathology. However, with both readers there is a general trend toward an underestimation of tumour size. The data was then analysed using the density categories, 1 (low density), and 2 (high density), to investigate whether there was better correlation between pathology and the size estimation with tomosynthesis in the lower density group.

3.4.2.2.2 DBT Average Tumour Size with Density

The database was analysed to assess the effect of breast density on measurement correlation. Two groups were created in accordance with standard description of breast density, namely Density Low, Category 1=A & B, and Density High, Category 2=C+D. These groups were compared with the average reader tumour measurements. There was a tendency toward a fatty breast composition in the cohort, with over 60% in Density Category 1 (A&B). Figures 3.8 and 3.9 show how increasing breast density can affect tumour size calculation, with poorer correlation in higher density categories. Spearman's rank coefficient $rs(64)=[.560]$, $p<.001$, for average DBT measurements for Density Category 1, and $rs(28)=[.371]$, $p=[.044]$, for Density Category 2 (Figure 3.8; Figure 3.9).

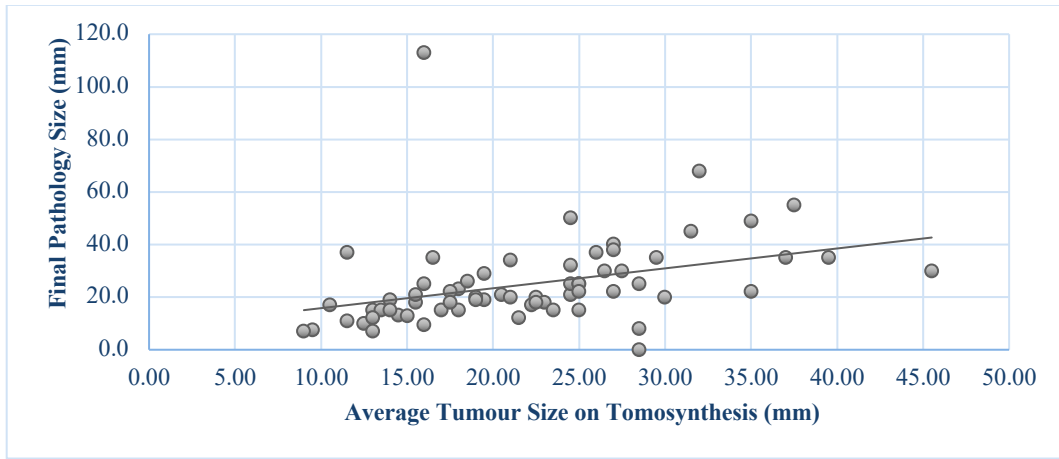


Figure 3.8 Average DBT and final pathology tumour size for density Category 1
 Note: Spearman's rank correlation $r_s(64) = [.560]$, [$p < .001$]

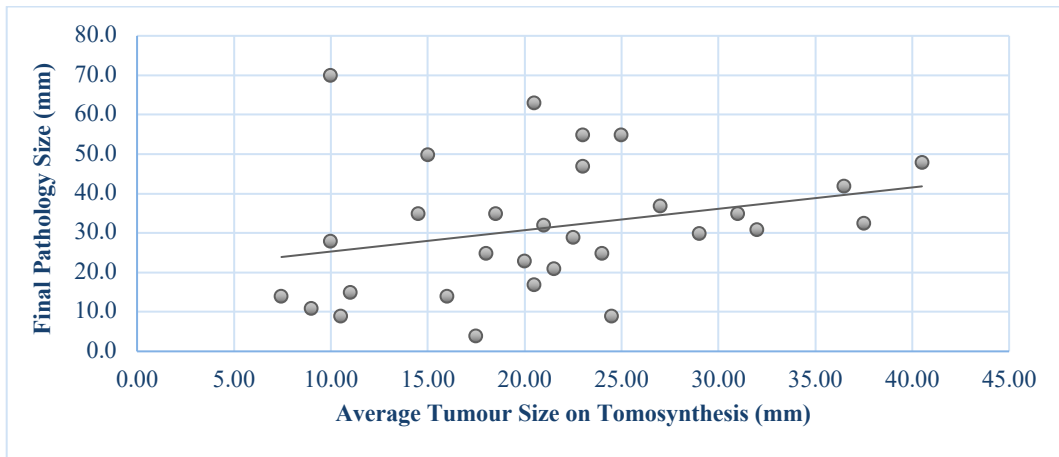


Figure 3.9 Average DBT and final pathology tumour size for density Category 2
 Note: Spearman's rank correlation $r_s(28) = [.371]$, [$p = .044$]

3.4.2.2.3 DBT Size Assessment by Tumour Size Group

Review of the dataset was performed to evaluate whether increasing tumour size may result in a reduction in imaging/histological correlation. The cohort was divided into two groups: T1, for tumour sizes of 20mm or less (Figure 3.10), and for tumours greater than 20mm (T2 & T3) (Figure 3.11). The size measurement on tomosynthesis was plotted against final histology size. Spearman's rank coefficient for T1 tumours $r_s(28)=[0.371]$, $p=[.036]$, for T2 and T3 tumours, $r_s(54)=[.164]$, $p=[.228]$.

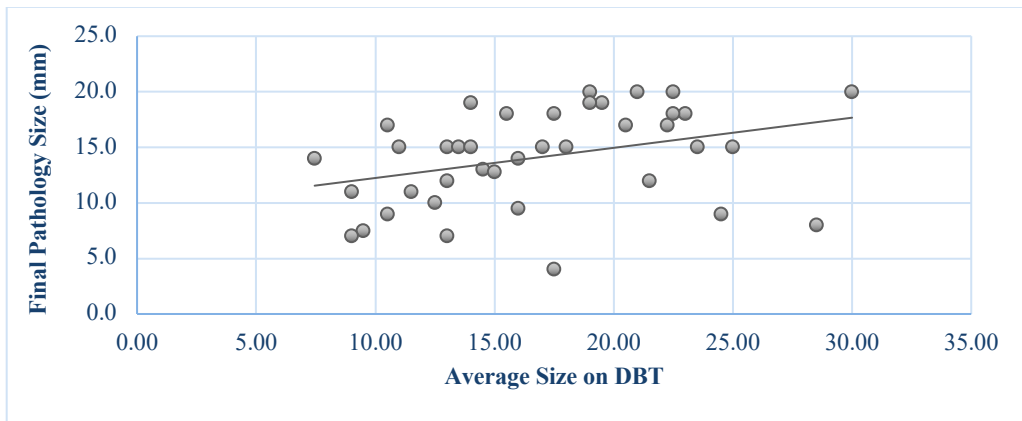


Figure 3.10 Tumour size on DBT for T1 lobular cancers.
 Note: Spearman's rank correlation $rs(38)=[.332]$, $p=[.036]$

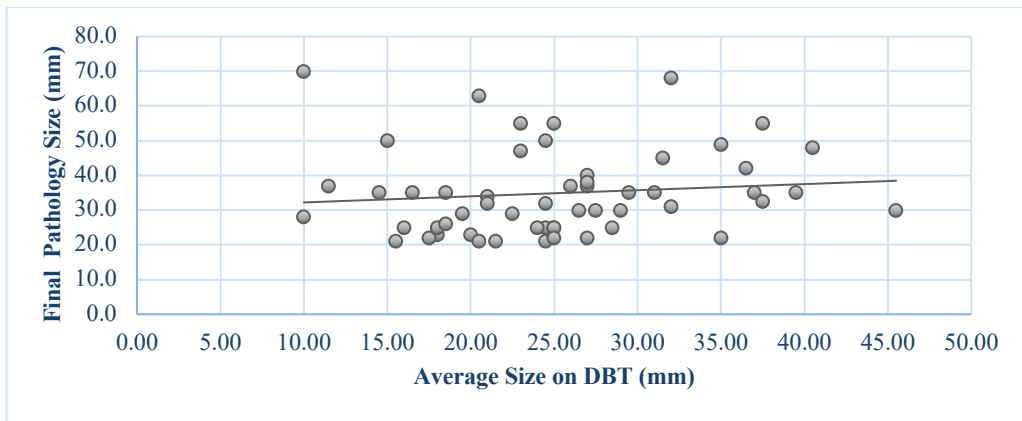


Figure 3.11 Tumour size on DBT for T2 and T3 lobular cancers.
 Note: Spearman's rank correlation $rs(54)=[.164]$, $p=[.228]$

Imaging evaluations for T2 and T3 tumours were combined for assessment. Patients with early breast cancer with large tumours on imaging preoperatively would normally be considered for mastectomy. All the individuals in this study were planned for conservative breast surgery. 7 of the cohort presented with tumours in the T3 category (Table 3.11).

Table 3-11 Characteristics of T3 lobular cancers

| Study No. | Age | USS Size | DBT 1 Size | DBT 2 Size | Mammographic Abnormality | DBT Density | MRI Size | Operation | Final Pathology Size |
|-----------|-----|----------|------------|------------|---------------------------------|-------------|-----------------------------|-----------------------|----------------------|
| 5†µ | 56 | 31 | 32 | 32 | Spiculated Mass | B | 65 | Mastectomy | 68 |
| 36µ | 55 | 6.2 | 21 | 20 | Distortion | C | 23.5 | Mastectomy | 63 |
| 40 | 56 | NS | NS | NS | Distortion with Calcifications | B | 22.5 | Mastectomy | 72 |
| 47µ | 49 | 10 | 10 | 10 | Mass with Distortion | D | 71 | Mastectomy | 70 |
| 67µ | 50 | 21.5 | 25 | 21 | Distortion with Calcifications | C | Occult. Nodal disease noted | Completion Mastectomy | 55 |
| 69µ | 58 | 18.6 | 23 | 27 | Mass | D | 35 | Mastectomy | 55 |
| 98µ | 72 | 9 | 10 | 22 | Spiculated Mass with Distortion | B | 70 | Mastectomy | 113 |

Note: †HER2 positive; µ axillary nodal involvement. Measurements in mm.

3.4.2.2.4 DBT Tumour size groups with ± 5mm thresholds

Tumour size correlation using a Radiologic-Pathological concordance defined as an imaging estimate within 5mm of the final pathological size was performed to reflect a more practice based approach. These tolerances were applied to the whole cohort to investigate the level of agreement between DBT measurements and size on final pathology for both Reader 1 and Reader 2. The results show that 44% and 51% of the tomosynthesis tumour measurements were within 5mm for Reader 1 and 2, respectively (Table 3-12).

Table 3-12 Agreement between DBT and final pathology for total cohort with 5mm Tolerance

| Cohort n = 103 Agreement with Final Pathology | DBT 1 n = 96 % agreement | DBT 2 n = 100 % agreement | DBT Averaged n = 96 % agreement |
|--------------------------------------------------|--------------------------------|---------------------------------|---------------------------------------|
| Within +/- 5mm | 44.0 | 51.0 | 48 |
| <5mm (underestimate) | 36.5 | 36.0 | 35 |
| >5mm overestimate | 17.7 | 13.0 | 13 |

Note: The DBT measurements of the whole cohort were compared with final pathology with 5mm tolerance (+/-) to estimate percentage agreement separately for both Readers and for the combined measurements. n=96 Reader 1, n=100 Reader 2 and combined n = 96.

As the findings suggested some level of agreement when tolerances of 5mm were applied to the measurements on tomosynthesis, with a combined reader agreement of 48%. The cohort dataset was then separated by tumour size, less than or equal to 20mm (T1) or greater than 20mm (T2 and above), to assess whether increasing tumour size affected agreement between tomosynthesis and pathology. The analysis was performed for each Reader separately as shown in Table 3-13 and 3-14.

Table 3-13 Agreement between DBT and final pathology with 5mm tolerance for T1 tumours

| Cohort Tumour Size | DBT 1 n = 40 % agreement | DBT 2 n = 42 % agreement | DBT averaged n = 40 % agreement |
|----------------------|--------------------------------|--------------------------------|---------------------------------------|
| < 20mm n=42 | | | |
| Within +/- 5mm | 67.5 | 71.5 | 67.5 |
| <5mm (underestimate) | 7.5 | 7.1 | 5 |
| >5mm overestimate | 25.0 | 21.4 | 27.5 |

Note: The data was analysed to assess whether the agreement between DBT and pathology improved for T1 tumours. 42/103 (40.78%) of the cohort had tumour sizes less than 20mm.

Table 3-14 Agreement between DBT and final pathology with 5mm tolerance for T2 and T3 tumours

| Cohort Tumour Size | DBT 1 n = 56 % agreement | DBT 2 n = 58 % agreement | DBT average n = 56 % agreement |
|----------------------|--------------------------------|--------------------------------|--------------------------------------|
| >20mm | | | |
| Within +/- 5mm | 30.4 | 36.2 | 37.5 |
| <5mm (underestimate) | 57.1 | 56.9 | 58.9 |
| >5mm overestimate | 12.5 | 6.9 | 3.6 |

Note: DBT assessment compared with final pathology for the whole cohort for tumour sizes greater than 20mm (n=58)

These results suggest that with increasing tumour size, the discrepancy between tomosynthesis measurements and final pathology increases. With T1 tumours (≤ 2 cm in size) the percentage agreement within the 5mm tolerance was 67.5%. However, with T2 and T3 tumours only 37.5% were within the 5mm threshold. Additionally, tumour size was underestimated in 58% of the T2 tumour group, but only in 5% of T1 cancers, while DBT overestimated lesion size in the T1 group in 27.5% of cases and 12.5% of the T2 and T3 tumours, suggesting a trend toward overestimating tumour size if the index lesion was 20mm or lower, and underestimation, if the cancer was over 20mm. This is especially evident for T3 tumours (Table 3-11).

The outliers were then removed from the analysis, with the dataset reinvestigated by tumour group size. There was a positive Spearman’s rho correlation coefficient between the variables, which was moderate for T1 tumours, $rs(37)=[.430]$, $p=[.006]$, and weak for T2 and T3 lesions, $rs(53)=[.217]$, $p=[.111]$.

3.4.2.2.5 The effect of breast density on mammographic tumour size assessments

The effect of breast density on tumour size assessment was investigated. DBT density was evaluated subjectively until 2015 when the Quantra system was added to the Hologic software in HDUHB. Tumour size categories were grouped into Density A+B as Category 1 (fatty), and C+D Category 2 (Dense), to assess the size agreement for the total cohort and evaluated with tolerances of +/-5mm for each Category. The differences in density recorded were prior to the introduction of the addition of the Hologic software, Quantra. Allocation of the patients to the Density Categories (Group 1 and Group 2) was the same for the readers. The discrepancy arose between C and D. However, this did not impact on the categorisation, as these were both in Group 2. Table 3.15 demonstrates the effect of increasing breast density on lesion measurement. These results suggest that with higher breast density, DBT underestimates tumour size, whereas, with low breast density (Category 1), tomosynthesis underestimates lesion size to a lesser degree.

Table 3-15 The effect of breast density on the size assessment by DBT

| Cohort Tumour Size | Density Category 1 n = 69 % agreement | Density Category 2 n = 30 % agreement |
|----------------------|---------------------------------------------|---------------------------------------------|
| Within +/- 5mm | 54.5 | 40.0 |
| <5mm (underestimate) | 28.8 | 53.3 |
| >5mm overestimate | 16.7 | 6.7 |

Note: The effect of breast density on size assessment with DBT comparing Category 1 (Density A+B) with Category 2 (C+D)

3.4.2.2.6 Analysis of mammographic abnormality and mammographic review

Mammographic findings such as distortion and asymmetrical densities can be difficult to accurately measure. These imaging features are more likely to be found with ILC than IDC. The imaging features of the cohort were reviewed (Table 3.16).

Table 3-16 Mammographic lesion descriptors noted in study cohort images

| MAMMOGRAPHIC FEATURES | N |
|-----------------------------------------------|----|
| Mass | 46 |
| Mass + calcifications | 1 |
| Spiculated Mass | 25 |
| Spiculated Mass associated with calcification | 1 |
| Architectural Distortion | 34 |
| Architectural Distortion with calcifications | 3 |
| Asymmetry | 0 |
| Asymmetry with calcifications | 1 |
| Calcifications with no mass or distortion | 3 |
| Normal Findings/Occult | 1 |

Note: Mammographic findings for whole cohort. The presence of more than one main feature was added as an additional count.

The most common mammographic abnormalities associated with ILC in this study, was a mass, or an architectural distortion. Evaluating tomosynthesis characteristics in the T3 group of tumours in the dataset (n=7), confirms that there were 3 masses with indeterminate margins, 3 architectural distortions, and 1 case with architectural distortion, mass, and asymmetry. The latter case imaging findings were noted in cohort number 98. The final tumour size on pathology was 113mm. There were significant imaging size discrepancies with sonography and tomosynthesis for both Readers 1 and 2, with size on ultrasound calculated at 9mm, and tomosynthesis measurements for Reader 1 and Reader 2, 10 and 22mm, respectively. Lesion size on MRI, 70mm, demonstrated greater concordance with final pathology. Review of the imaging in this case highlights the difficulties presented to the clinician when assessing patients with ILC, with greater size discrepancy noted at final histology. The MRI directed the management toward mastectomy, which was justified in this case, as the tumour extent was 113mm.

One case in the cohort was occult on both tomosynthesis and sonography (Case no. 56). The patient, a 37 year old women, presented with contralateral breast pain and

was noted to have a few indeterminate calcifications on the right breast tomosynthesis images with normal ultrasound findings. Breast density D (very dense). DBT guided biopsy confirmed the presence of lobular breast cancer. MRI measurement of the index lesion was 35mm. As the patient had a small breast volume, she underwent a mastectomy with immediate reconstruction. Final pathology confirmed a 28mm Grade 2 ILC. This case was image detected on tomosynthesis owing to the presence of a few microcalcifications. However, the main tumour mass was not seen on standard imaging, only on MRI. This highlights the importance of further imaging in ILC especially in young patients with dense breast tissue.

The presence of microcalcification with lobular cancers is not common. In this study, calcification was the only abnormality noted on tomosynthesis in 3 cases (2.91%). In the total cohort n=103, calcification was seen in 11/103 (10.68%) of the tomosynthesis images. Calcification can be seen in association with DCIS or LCIS. Review of the findings in the three patients with LCIS found on preoperative biopsy or on final histology is shown in Table 3-17. These patients were all from the screening cohort. Although, it is not common to see calcifications on mammograms of patients with lobular cancer, if there is preinvasive pathology present within the breast, this may be seen as suspicious calcification.

Table 3-17 Imaging and pathology of ILC associated with Lobular Carcinoma in-situ

| Case Number | 24 | 70 | 101 |
|-------------------------------------------------|-----------------------------------------|----------------------|------------------|
| Age (years) | 51 | 70 | 50 |
| Breast Density Category | B | C | B |
| Imaging Finding on DBT | Calcification | AD/calcification | AD/calcification |
| Size on USS | Occult | 14.7 | 16 |
| Size on DBT Reader 1 | 33 | 25 | 16 |
| Size on DBT Reader2 | 24 | 17 | 21 |
| Size on MRI | 42 | 13+33 multifocal | 16 |
| Final Pathology Size of Invasive Lobular Cancer | No size. | Multifocal ILC 16+16 | 21 |
| Final Pathology Size of LCIS | Multifocal LCIS only on final pathology | 30mm LCIS | 70mm LCIS |

Note: Details of the three screen detected cases diagnosed on tomosynthesis with LCIS on final pathology. Sizes in mm.

3.4.2.3 Sonography Measurements`

Sonography is performed on all patients in the symptomatic setting. It is widely available and is a valuable tool in the assessment of index lesions and for guiding biopsies. The typical appearance of ILC on ultrasound is of a hypoechoic mass or distortion.

The cohort with ultrasound images and measurements was 83. Aside from missing images, there were 3 cases where the sonographic assessment was normal. These were the tumours that were detected owing to the presence of pleomorphic malignant calcification. ILC lesion measurement ranged from 4.5mm to 35.4mm on sonography, compared with 4mm and 113mm on Pathology. The median tumour size on sonography was 14.20mm, compared with 22mm on final pathology (Table 3.18).

Table 3-18 Median tumour size by pathology and sonography for whole cohort

| n=83 | Percentiles | | |
|-------------------------------------------|------------------|---------------------------|------------------|
| | 25 th | 50 th (Median) | 75 th |
| USS Size mm (min 4.5/max 35.4) | 10.60 | 14.20 | 18.60 |
| Final Pathology Size mm | 15.00 | 22.00 | 35.00 |

Note: Descriptive statistics of the cohort with sonographic measurements (n=83)

As stated above, the dataset was not normally distributed. The measurements on USS and pathology were investigated to assess correlation using Spearman’s rank correlation testing. The results confirms that there is only a weak correlation between sonography and pathology measurements in this lobular cohort (Figure 3.12), $rs(81)=[.355], p<.001$.

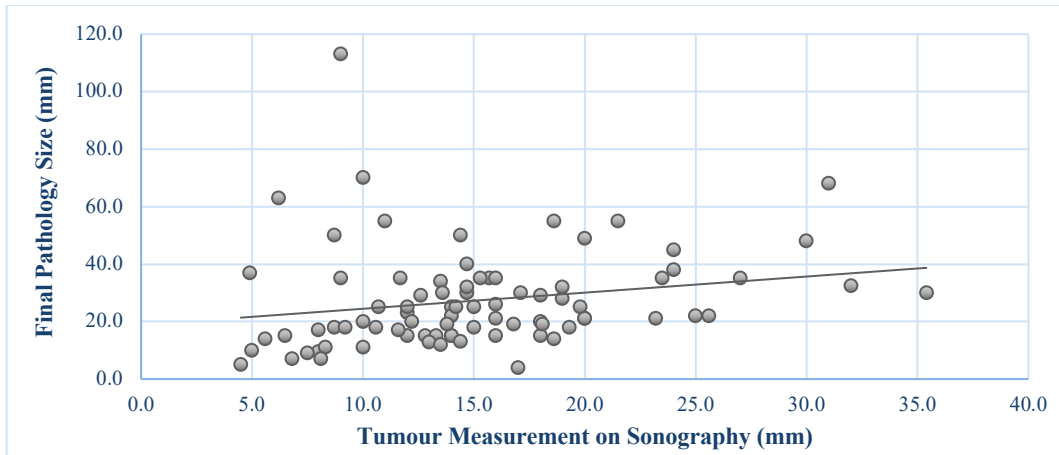


Figure 3.12 Tumour size on sonography and final pathology for total cohort.
 Note: Cohort n= 83. Spearman’s rank correlation $rs(81) = [.355]$, $p < .001$

3.4.2.3.1 Effect of tumour size on sonographic measurements

The dataset was separated into T1 (n=35) and T2+ T3 (n=48) tumours to evaluate whether size discrepancy on sonography increased with tumour size (Figure 3.13 & Figure 3.14). The mean tumour size in the T1 group on ultrasound and pathology was 11.95mm and 14.29 respectively. The size in the T2 group was 17.36mm for USS and 36.8mm for pathology, suggesting that sonography underestimates lesion size, especially for larger tumours. This is highlighted in the results of Spearman’s rank correlation testing, with tumour measurement for lesions 20mm or less, $rs(33)=[.409]$, $p=[.15]$ (Figure 3.1.3), and a negative correlation, $rs=[-.151]$, $p=[.306]$, for the larger tumours (Figure 3.1.4).

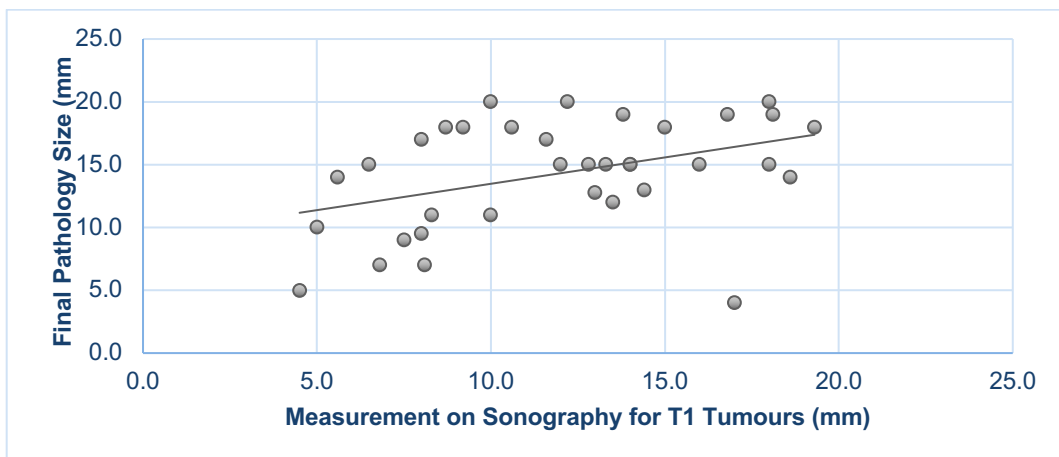


Figure 3.13 Size on sonography and final pathology for T1 tumours
 Note: Spearman’s rank correlation $rs(33)=[.409]$, $p=[.015]$

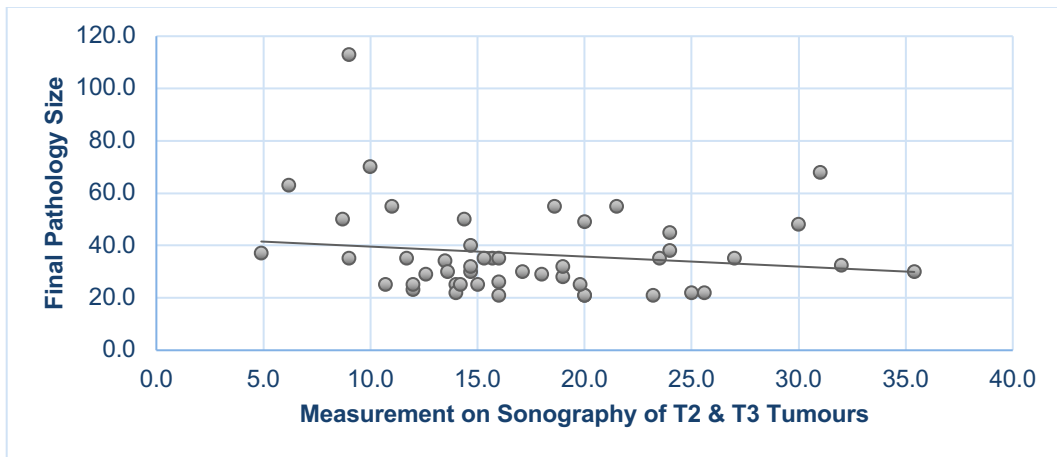


Figure 3.14 Size on sonography and final pathology for T2 and T3 tumours
 Note: Spearman’s rank correlation $r_s(46) = [-.151]$, $p = [.306]$

3.4.2.3.2 Effect of breast density on sonographic size assessment

The sonographic measurements were evaluated according to breast density, as categorised on tomosynthesis, to investigate the effect of breast density on tumour measurement, with Spearman’s rank correlation calculated for both density groups (Table 3.19).

Table 3-19 Sonographic tumour measurements by breast density

| | Sonography | Pathology |
|-------------------------------------------------|-----------------------------|-----------|
| Median Size (mm) | 14.2 | 22 |
| Interquartile Ranges | 8.0 | 20.0 |
| Correlation Coefficient Density Group 1 n=62 | $r_s = .384$ ($p = .002$) | |
| Correlation Coefficient Density Group 2 n=21 | $r_s = .244$ ($p = .287$) | |

These results suggest that increasing breast density reduced size agreement on sonography. This will be further explored in 3.5.

3.4.2.4 MRI

MRI descriptive statistics confirmed that the dataset was not normally distributed. The median tumour size on MRI and final pathology was 23.00 (IQR 17.00) and 23.00 (IQR 20.00), respectively. There was no cancer in one of the final pathology specimens included in the analysis, with 102 MRI tumour measurements. The cohort size for analysis was 101. Spearman’s rank correlation was computed to assess the relationship

between the size assessment with MRI and final pathology. Spearman's rho testing suggested a strong positive correlation between the two variables, $r_s=[.608]$, [$p<0.001$] (Figure 3.15). There are several outliers at the extremes of pathology measurements.

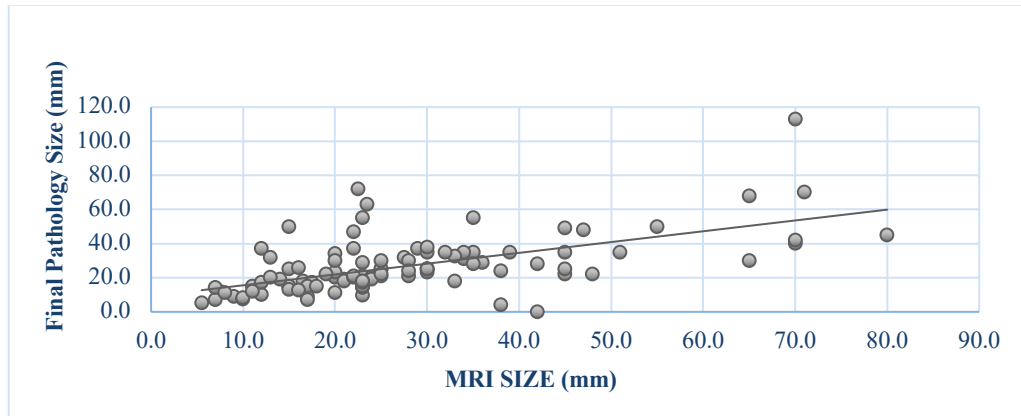


Figure 3.15 Tumour size on MRI compared with final pathology.

Note: Spearman's correlation coefficient $r_s(99) = [.608]$; [$p<0.001$]

3.4.2.4.1 Effect of tumour size on MRI measurements

The analysis was repeated for tumour sizes T1 (less or equal to 20mm) and T2 and T3 (greater than 20mm). These results suggest that ILC size assessment with MRI has moderate strength correlation with final Pathology for tumours that are 20mm or smaller, $r_s(40)=[.450]$, $p=[.003]$ (Figure 3.16). However, there is greater discrepancy with large tumour size, with weak correlation $r_s(56)=[.237]$, $p=[0.07]$ for T2 and T3 tumours (Figure 3.17).

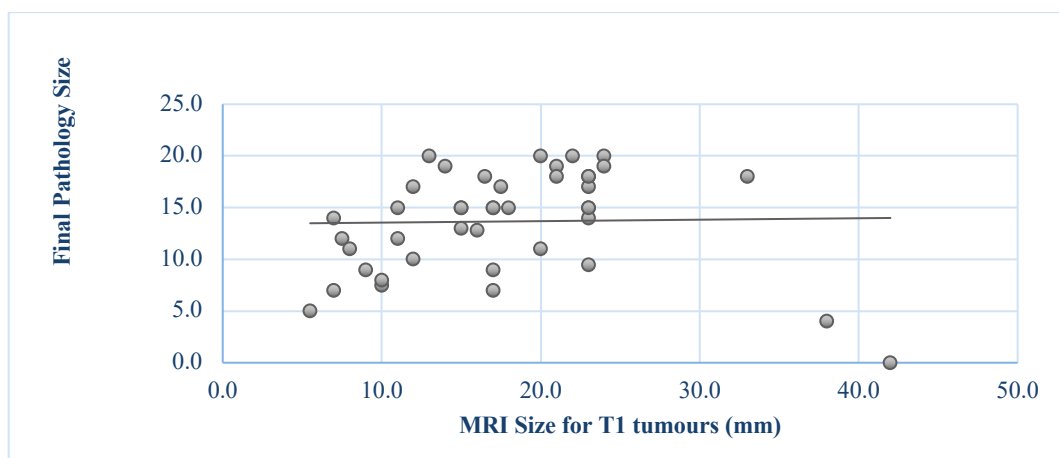


Figure 3.16 Tumour measurement on MRI for T1 tumours

Spearman's rho Correlation Coefficient $r_s(40) = [.450]$, [$p=0.003$]

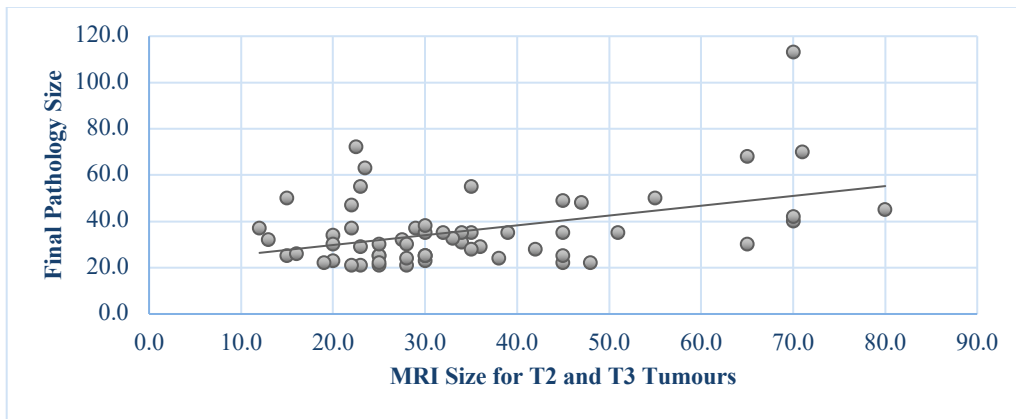


Figure 3.17 Tumour measurement on MRI for T2 and T3 tumours
Spearman's rho Correlation Coefficient $r_s(56) = [.237]$, $[p=0.073]$

When the dataset for tumour group size was analysed, a reduction in the degree of correlation between measurements on MRI and pathology was observed. The strength of the correlation appeared to be reduced by the presence of significant outliers. After excluding outliers, cohort numbers 24, and 98, pathologies with extensive DCIS and LCIS respectively, Spearman's rho correlation coefficient for MRI for T1 tumours was $r_s(40)=[.450]$, $p=[.003]$, and for T2 plus T3, $r_s(56)=[.237]$, $p=[.073]$, suggesting that there was a weaker correlation between MRI and pathology with the larger lobular tumour sizes.

3.4.2.4.2 Effect of breast density on MRI size assessment

The dataset was reviewed further to assess the effect of breast density on MRI measurement. Spearman's rho correlation coefficient demonstrates a strong relationship between pathology and MRI for the lower density group (Category 1), with only a moderate relationship for the dense group (Category 2) (Table 3.20).

Table 3-20 Spearman's rho Correlation Coefficient for MRI and final pathology by Density Group

| Density Category | Modality | Spearman's rho correlation coefficient | Significance | Number |
|------------------|------------------------|----------------------------------------|--------------|--------|
| 1 | Final Pathology MRI | $r = .659$ | $p < .001$ | 68 |
| 2 | Final Pathology MRI | $r = .442$ | $P = .010$ | 33 |

3.4.2.5 Multiple Linear Regression Testing

As a final analysis, multiple linear regression testing was performed on the dataset, with the assistance of Dr Mike Kiernan. The size of the final cohort, after removing cases with one or more missing values in the imaging values (sonography, tomosynthesis, and MRI), plus one in pathology, was $n=78$. For the multiple linear analysis, outliers with large discrepancies between tumour and final pathology size were identified ($n=2$). The imaging and case notes were reviewed. For the multiple linear regression analysis, these two cases were excluded, as they were considered extreme cases of the population.

Matrix plots with fitted linear regression lines were created to confirm that the measurements from the imaging modalities and final pathology were linearly related to each other (Figure 3.18). The matrix plot in Figure 3.18, with fitted linear regression lines, suggested that the four modalities chosen to measure tumour sizes were all linearly related to each other justifying the use of multiple linear regression analysis.

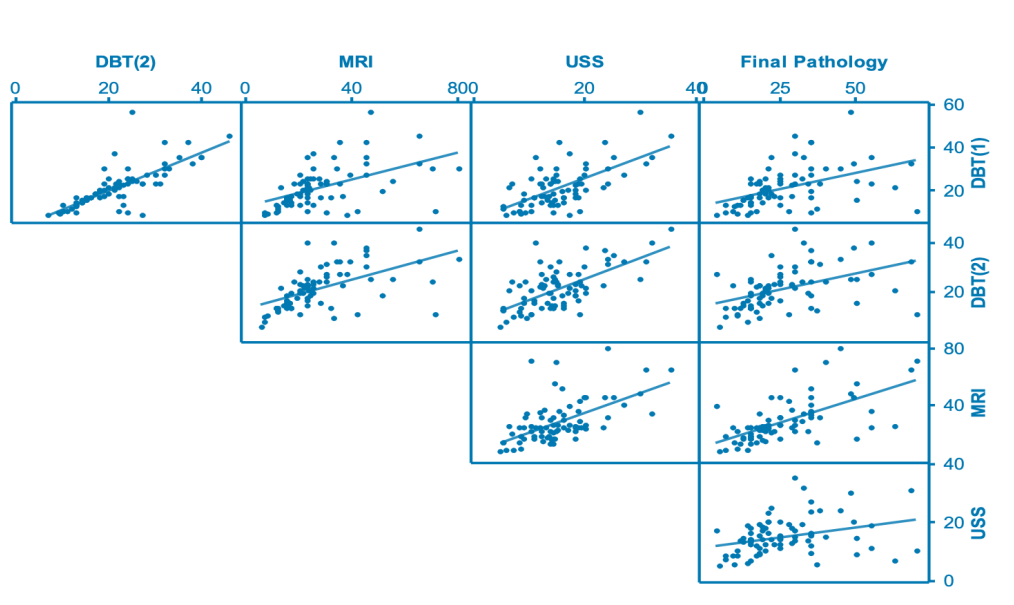


Figure 3.18 Matrix plots for tumour size assessment with pathology, tomosynthesis, MRI and sonography

Constructing the error bar chart shown in Figure 3.19 suggested that the mean size measurement (M) of the tumours were smaller when using USS ($M=15.0$ mm); and DBT ($M=21.1$ mm), when compared with MRI ($M=27.5$ mm) and Final Pathology ($M=26.1$ mm).

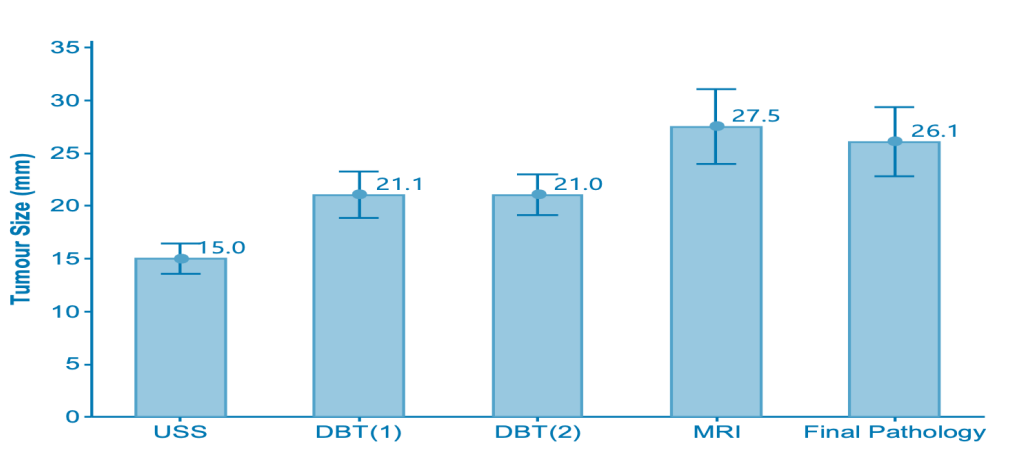


Figure 3.19 Tumour size estimates by imaging modality

Note: The vertical error bars symbolized by \lrcorner , drawn either side of the mean value symbolized by \bullet , reflect the precision of the tumour size measurements.

The analysis was then repeated to investigate the effect of age on tumour size assessment. The results in Figure 3.20 suggest that tumour size was higher in the younger patient with all imaging modalities.

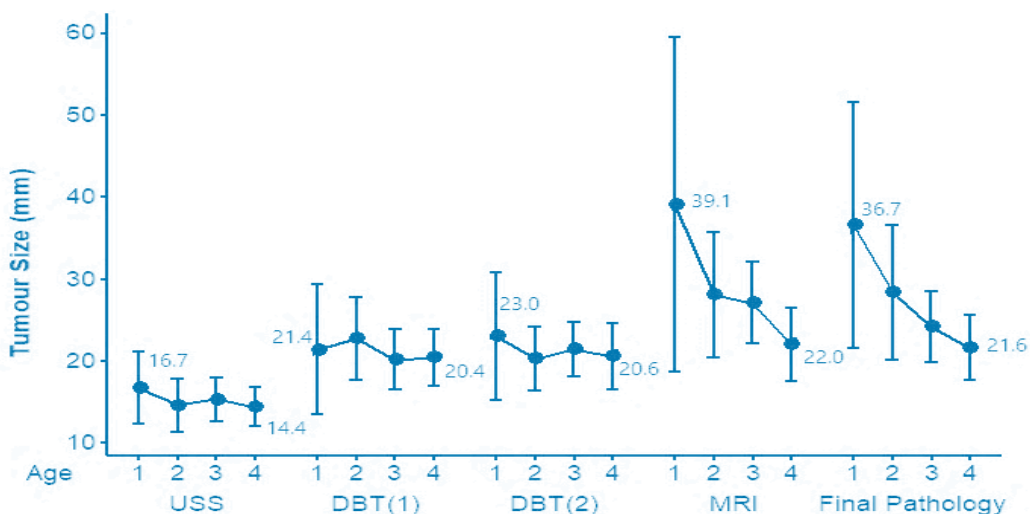


Figure 3.20 Tumour size assessment by modality analysed by age category.

Note: Age groups (years): 1 = 38 to 50; 2 = 51 to 59; 3 = 60 to 69; 4 = 70 to 80

As breast density is a recognised factor in size discordance in imaging, the dataset was analysed to investigate the effect of density on measurements. Figure 3.21 illustrates tumour mean size estimation with the four modalities, with each density Category.

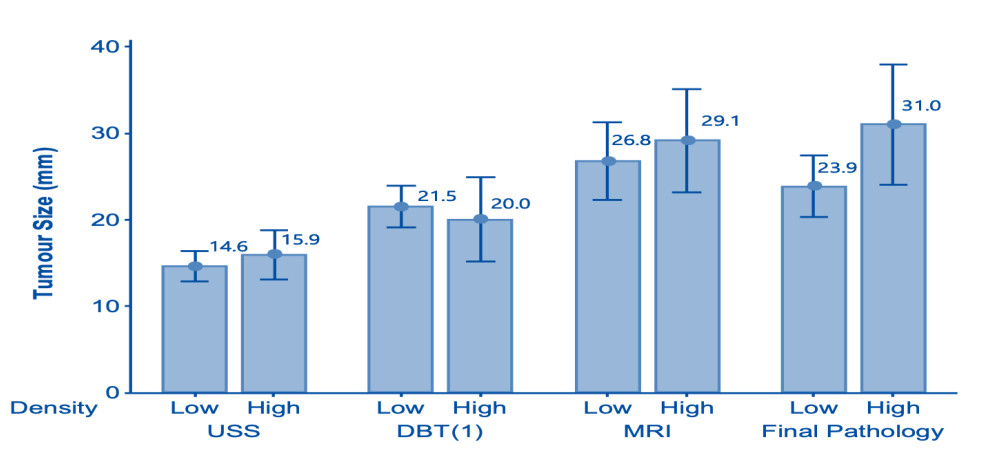


Figure 3.21 Tumour size measurement for each modality analysed by mammographic density.

Multiple linear regression testing of the dataset suggested that the imaging modality that provided the most accurate estimate of tumour size at histology was MRI (Figure 3.22). MRI tumour measurements had the smallest mean difference (M_D) relative to the gold standard ($M_D = -1.23$ mm). The lower accuracy of DBT was indicated by $M_D=5.4$ mm for Reader 1, and $M_D=5.0$ mm for Reader 2. USS provided the least accurate estimate of tumour size ($M_D=11.1$ mm). The narrower widths of the error bars (95% CI ± 0.48 mm) indicate that the MRI measurements were more accurate and precise than the measurements made with DBT (95% CI ± 3.4 and ± 2.9 mm) and USS (95% CI ± 3.2 mm).

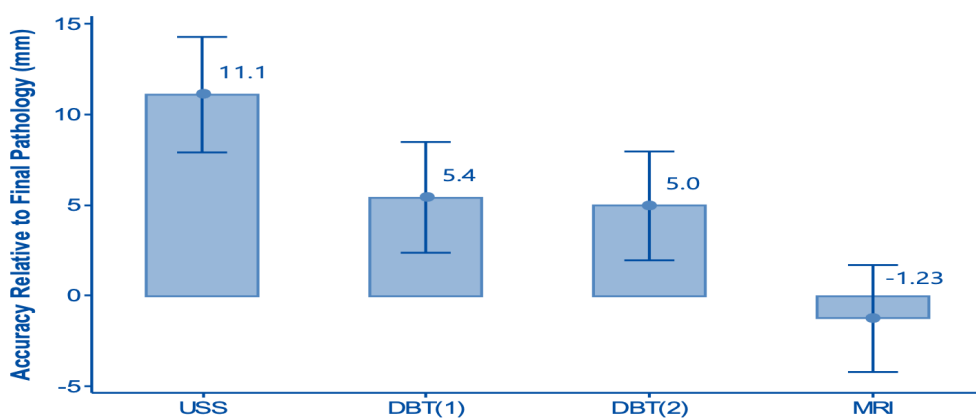


Figure 3.22 Accuracy of tumour size assessment with each imaging modality

The effect of breast density on size assessment with each modality can be seen in Figure 3.23. As breast density increases, the difference in tumour assessment with both sonography and mammography relative to pathology, also increases (Figure 3.21).

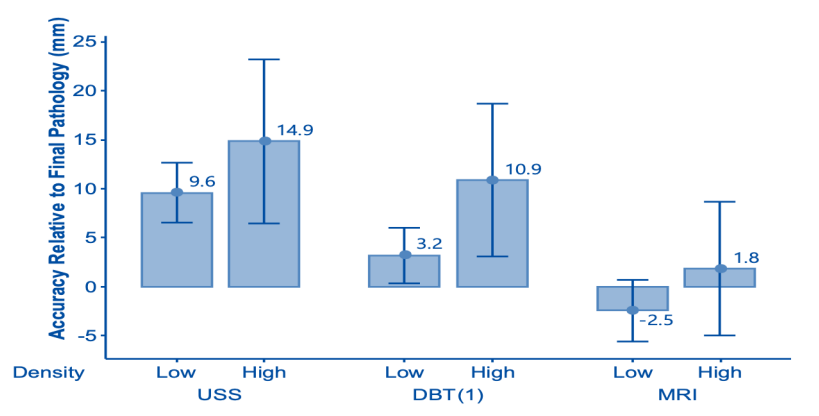


Figure 3.23 Tumour size measurements by imaging modalities by breast density

Note: The tumour size assessments with each modality relative to final pathology for each density category (Low 1= A&B; High 2= C&D).

Multiple regression analysis confirmed that the accuracy of average DBT measurements in the low density category compared with MRI was moderate, R^2 .332 (95% CI .164 to .502), β =.446 (Table 3.21). This was repeated for density category 2, R^2 .365 (95% CI .193 to .532), β =.484 (Table 3.22).

Table 3-21 Multiple Regression Analysis DBT and MRI with Covariates for Density Category 1

| Variable | B | β | (95% CI) of β | | P | R ² (95% CI) | 95% CI R ² | |
|----------------------------|--------|---------|---------------------|-------|-------|-------------------------|-----------------------|-------|
| | | | Lower | Upper | | | Lower | Upper |
| Constant | 19.012 | -.004 | -.196 | .189 | .970 | .332 | .164 | .502 |
| Accuracy MRI | .454 | .446 | .247 | .640 | <.001 | | | |
| Age (Years) | -.342 | -.243 | -.434 | -.049 | .015 | | | |
| Tumour Density (Category1) | 6.431 | 0.226 | .028 | .425 | .026 | | | |

Table 3-22 Multiple Regression Analysis DBT and MRI with Covariates for Density Category 2

| Variable | B | β | (95% CI) of β | | P | R ² (95% CI) | 95% CI R ² | |
|-----------------------------|--------|---------|---------------------|-------|-------|-------------------------|-----------------------|-------|
| | | | Lower | Upper | | | Lower | Upper |
| Constant | 18.555 | .000 | -.185 | -.185 | 1.000 | .365 | .193 | .532 |
| Accuracy MRI | 0.4900 | .484 | .296 | .672 | <.001 | | | |
| Age (Years) | -0.328 | -.234 | -.424 | -.044 | .017 | | | |
| Tumour Density (Category 2) | 5.993 | .209 | .018 | .401 | .033 | | | |

The analysis was then repeated with average DBT measurements and sonography suggesting that tomosynthesis and sonographic measurements were closely associated, especially in dense breast tissue (Category 2) (R².808 (95% CI .714 to.874), β .000, p <.001 (Table 3.23; Table 3.24).

Table 3-23 Multiple Regression Analysis DBT and Sonography with Covariates Density Category 1

| Variable | B | β | (95% CI) of β | | P | R ² (95% CI) | 95% CI R ² | |
|---------------------------|--------|---------|---------------------|-------|-------|-------------------------|-----------------------|-------|
| | | | Lower | Upper | | | Lower | Upper |
| Constant | -6.810 | -.147 | -.124 | .107 | .884 | .760 | .648 | .840 |
| Accuracy USS | .778 | .825 | .696 | .937 | <.001 | | | |
| Age (Years) | -0.034 | -.024 | -.142 | .095 | .690 | | | |
| Tumour Density Category 1 | 4.290 | .251 | .032 | .270 | .013 | | | |

Table 3-24 Multiple Regression Analysis DBT and Sonography with Covariates Density Category 2

| Variable | B | β | (95% CI) of β | | P | R ² (95% CI) | 95% CI R ² | |
|---------------------------|--------|---------|---------------------|-------|-------|-------------------------|-----------------------|-------|
| | | | Lower | Upper | | | Lower | Upper |
| Constant | 7.437 | .000 | -.102 | .102 | 1 | .808 | .714 | .874 |
| Accuracy USS | .797 | .847 | .741 | .953 | <.001 | | | |
| Age (Years) | -0.041 | -.029 | -.136 | .077 | .583 | | | |
| Tumour Density Category 2 | 4.823 | .170 | -.136 | .065 | .275 | | | |

3.5 DISCUSSION

Evidence for the use of breast tomosynthesis in both the breast screening and symptomatic sector is well established. As studies have shown that tumour margin visibility is enhanced with the technology, assessment of lesion size has also improved when compared with standard digital mammography (Caumo et al., 2018; Raghu et al., 2016). However, most studies have included all cancer subtypes, such that the evidence for the second most common breast cancer, lobular cancer, is often extrapolated as a secondary analysis from prospective trials. Lobular breast cancer, which accounts for less than 15% of all breast cancer diagnoses, can be difficult to detect on standard imaging, and is often occult, such that magnetic resonance imaging is required prior to surgery. Based on the evidence from studies that preoperative assessment in all tumour subtypes is improved with DBT, this study evaluated the use of tomosynthesis in patients with ILC, comparing imaging size estimation with MRI.

A prospective multicentre study was initially considered. However, this was not feasible in the timeframe and costs were deemed to be prohibitive. A retrospective two-reader blinded study was therefore conducted in a population of patients who were diagnosed with lobular breast cancer and planned for conservative breast surgery. The sample size, $n=103$, although consistent with that seen in the literature, was affected by missing images from all modalities. Another factor limiting sample size was the relatively high mastectomy rates in the peripheral hospitals in HDUHB, partly a consequence of population demographics in the more remote parts of Southwest Wales, coupled with the travelling distance for adjuvant radiotherapy, often resulting in patients opting for a mastectomy rather than conservative breast surgery, thereby obviating the need for MRI. In addition, during the pandemic, more patients opted for a mastectomy rather than conservative breast surgery. Anecdotally, patients did not want a second operation, and did not want to travel for adjuvant radiotherapy, which resulted in a reduction in the number of MRI studies performed. However, the final sample size ($n=103$) is larger than many of the cohorts in the published research, and, in addition, after removing significant outliers, and missing values from one or more of the imaging modalities, the sample of 78 allowed adequate statistical power to conduct multiple linear regression analysis (Mokkink et al., 2023).

The cohort demographics in this investigation are similar to those found in the literature. Lobular cancer is less common in younger women (Arpino et al., 2004; Colleoni et al., 2012; Oesterreich et al., 2022; Pestalozzi et al., 2008), a factor also noted in our study, with 92.26% of the cohort being over 50 years of age. The mean age of the study group was 61.9 years (range 32 to 83), with only 8.74% (n=9) women under the age of 50 included in the analysis. The mean age of this cohort is consistent with the UK national incidence of breast cancer (Cancer Research UK, 2016–2018). However, the age range of this study may be geographically unique, and, as such, needs to be taken into context. As stated above, although the population in Southwest Wales is relatively homogenous, the effects of the pandemic may have resulted in a higher proportion of women opting for mastectomy, and, in addition, an increased number of patients received primary adjuvant endocrine therapy. As the inclusion criteria was lobular cases who did not receive neoadjuvant treatment, and who were planned for MRI and conservative breast surgery, this may have potentially skewed the age data, as some of the older patients opted for primary endocrine therapy.

3.5.1 Surgical Management

The cohort was evenly divided between screened to symptomatic patients, 45.63% and 54.3%, respectively. The operative details of the cohort confirm that MRI changed the surgical management in 43.69% of the total cohort, with 48.21% of the symptomatic sector and 29.79% from screening, undergoing a mastectomy. The latter figure is not surprising given that screen-detected tumours tend to be smaller than cancers diagnosed in the symptomatic setting (Starikov et al., 2021; Welch et al., 2016), and are therefore more suitable for conservative surgery.

Review of the published literature suggests that mastectomy rates for ILC are generally higher for this subtype of breast cancer, with some older studies quoting mastectomy rates of 70% (Moore et al., 2000; Pestalozzi et al., 2008), although more recent investigations report similar findings to this study, with mastectomy rates of between 37.4% to 57% (Amin et al., 2021; Moloney et al., 2020; Parvaiz et al., 2016; Selvi et al., 2018). The higher incidence of mastectomy rates seen in the literature is in part related to tumour size, which is often larger than IDC at presentation, when compared

with ILC (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008). This is particularly relevant in the younger patient, as findings of this study reflect those from other publications, suggesting that lobular cancers are often larger in the younger breast cancer patient, with tumour sizes greater than 20mm, resulting in a higher incidence of involved margins requiring further surgery and/or mastectomy for disease extent (Arpino et al., 2004; Dillon et al., 2006; Moloney et al., 2020; Moore et al., 2000; Oesterreich et al., 2022; Pestalozzi et al., 2008; Van Deurzen., 2008).

As mentioned above, the mastectomy rate of the whole cohort was 43.69%, with a higher rate of mastectomy (77.78%) seen in women under 50. Review of the tomosynthesis data on these younger patients suggests that in the cases converted to mastectomy (7/9), MRI overestimated disease extent, while DBT underestimated tumour burden. Other studies have noted this, suggesting that an extensive in-situ component in the pathology, large tumour size, or hormonal status may influence assessment of tumour extent in lobular breast cohorts (Gest et al., 2020; Mann et al., 2008; Rominger et al., 2016). The pathology of the dataset of the outliers was reviewed confirming that in this study, these cases were associated with an in-situ component (DCIS in 1 case, and extensive LCIS in the others). Additionally, as large population studies have shown that age is another factor that has been found to increase the risk of compromised margins in lobular breast cancer, especially in dense breast tissue, with data suggesting that mastectomy is often required in the younger patient (Dillon et al., 2006; Oesterreich et al., 2022; Pestalozzi et al., 2008).

A UK study recently investigated the effect of preoperative breast MRI on the surgical management of lobular cancer in a symptomatic population, and noted the factors that influenced surgical treatment were dense breast tissue and younger patients (Moloney et al., 2020). The authors suggest that preoperative MRI may be better directed for effectiveness. This is consistent with the findings of this study. Spearman's correlation indicated a lower association between the size assessment by MRI and pathology in the dense breast category, $r_s(31)=[.442]$, $p=[.010]$, compared with $r_s(66)=[.659]$, $p<.001$ in the group with a fatty composition. Indeed, this was even more pronounced when investigating the correlation between pathology and the standard imaging modalities, tomosynthesis and sonography. With increasing breast density, the correlation reduced from $r_s(64)=[.560]$, $p<.001$, to $r_s(28)=[.371]$, $p=[.044]$ with

tomosynthesis, and $rs(60)=[.384]$, $p=[.002]$, to $rs(19)=[.244]$, $p=[.287]$ for sonography, with significant underestimation of tumour size with both imaging modalities. Similar findings are well documented in the literature, (Chudgar et al., 2017; Förnvik et al., 2010; Förnvik et al., 2018; Mariscotti et al., 2014; Ozcan et al., 2023). The proposition by Moloney et al (2020), is worth considering, although the results of this research found only a moderate correlation between pathology and MRI in dense breast tissue, with strong correlation in the fatty breast tissue group of patients. A larger cohort number with younger women would be needed to investigate this further, as only a third of the patients in the cohort were in the dense category grouping.

3.5.2 Analysis of Final Pathology

The lobular histomolecular characteristics of this cohort are similar to those found in the literature. 99.03% of the tumours expressed *ER*, with most expressing *PR* (82.52%). Three of the tumours overexpressed *HER2*, these patients were from the early part of the study when neoadjuvant chemotherapy was not standard practice in HDUHB. The NPI and systemic inflammatory indices, NLR, PLR, MLR, SII, were calculated for the total cohort. In addition, Oncotype DX® RS testing was performed on 33 lobular cancers during the study period. The NPI scores were mainly in the intermediate risk group (59.22%), with only 2 patients in the high risk category. This has been noted in the literature (Engstrøm et al., 2015; Iorfida et al., 2012; Rakha et al., 2008), and is explored further in Chapter 4. One component of the index calculation is tumour grade, and as most ILC cancers are Grade 2, the NPI score is commonly in the moderate risk group (Rakha et al., 2008). This was also seen in the RS results, with 32 of the 33 lobular tumours tested having $RS \leq 25$, consistent with Oncotype DX® RS results in the literature (Makower et al., 2022). The mean range of the systemic inflammatory indices assessed were all in the normal range, as defined by the population study referenced (Fest et al., 2018; Forget et al., 2017). During the investigation period, there were 7 recorded deaths. Three patients developed bone metastases, one of whom, also developed liver metastases. The other deaths were non-breast related (Table 3.4). Of note, one of the deaths was in a patient with *BRCA2* mutation, a germline mutation most often associated with lobular cancer (Dossus &

Benusiglio, 2015). There were two patients in the cohort with *BRCA2* mutations, and 7 with a strong family history but with no mutation identified in 6-panel gene testing. During the period of this study, five histopathologists reported the breast biopsy samples, which may have introduced some bias in the pathology assessment. There are recognised challenges in the standardisation of the measurement of tumour pathology size aside from issues related to interobserver difference (Varma et al., 2014). The tumour may be associated with large areas of DCIS or LCIS, such that, accurate measurement of the invasive component may be problematic, as it is well documented that increasing tumour size can be difficult to measure accurately on histology (Varma et al., 2014). However, the two outliers with significant size discrepancies in this study were not associated with an in-situ component. The presence of in-situ pathology was only noted in 10 cases (9.71%). This is also consistent with the literature which has found that in-situ disease is more common in the presence of IDC (Tabár et al., 2022).

Studies have consistently shown how tumour size is often larger in the lobular subtype compared with IDC (Oesterreich et al., 2022). Mean tumour sizes on ILC pathology of 20mm to 28.6mm are often quoted in the literature (Chung et al., 1997; Pestalozzi et al., 2008). In this study, the tumour sizes ranged from 4mm to 113mm, mean 27.1mm, with no cancer seen in one final pathology sample, the invasive component having been removed during the diagnostic VAB. Of the cohort, 36.27% of the lobular cancers were T1 (≤ 20 mm), 54.9% were T2 (>20 -50mm), and 0.88% (9/102) were T3 (>50 mm). Two of these latter cases were outliers, with large discrepancies between final tumour size and imaging estimates for all modalities. The symptomatic cohort presented with tumour sizes that were larger than those seen in the screen detected patients. This is an expected finding which is well recognised in both clinical practice and in the published literature (Wishart et al., 2008). The tumour size distribution between the populations is consistent with other studies, with over half of the lobular tumours in screening being T1, and 69.64% in the symptomatic cohort being T2 (Starikov et al., 2021; Welch et al., 2016).

The introduction of breast screening has resulted in an almost 50% reduction in the size of breast cancers, with figures in the literature suggesting that number of T2 tumours (20mm or greater) decreased from 64% to 32% (Welch et al., 2016). This

figure may have reduced further, as the SEER data analysed was from 1975 to 2012. The results in this study demonstrate that the mean tumour size in the screened cohort (n=47) was 22.18mm, with 51.06% of the cohort 20mm or less (T1), 42.55% >20 to 50mm (T2), and 6.38% larger than 50mm (T3). Lobular breast cancer is often larger at presentation than other breast subtypes (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008), this potentially has upstaged our cohort compared with the findings in the literature. In addition, the population of Southwest Wales is screened from 50 years of age with triennial mammograms, such that direct comparison with the yearly assessments in many of the international studies is difficult.

3.5.3 Tumour Size on Imaging

Preoperative tumour size assessment is important in treatment planning. Standard breast imaging often underestimates tumour size and extent in patients with lobular breast cancer (Gruber et al., 2013; Nonnemacher et al., 2023; Vijayaraghavan et al., 2018), with MRI overestimating the disease (Moloney et al., 2020; Parvaiz et al., 2016; Selvi et al., 2018). The results of this study are consistent with the literature, as ILC size was underestimated by both sonography and tomosynthesis. The mean tumour size on sonography, DBT Reader 1 and DBT Reader 2, were 15.1, 21.27 and 21.47, respectively. This compares with the mean tumour size on MRI and pathology of 27.7 and 27.1, respectively. The underestimation of tumour size by sonography is more pronounced, with a mean of 12mm in this study, compared with figures reported in the literature of 8mm (Gruber et al., 2013; Luparia et al., 2013). Of note, within the dataset, three cases were large tumour sizes, and it is possible that these may have skewed the results. In addition, sonographic measurements are taken in real-time, and the size estimations from screening were taken by different sonographers and radiologists. This can result in systematic error. It can be difficult to delineate lesion edges and cursor placement can vary between observers (Berg, et al., 2000; Berg, et al., 2006; Kopans, et al., 2008; Skaane, et al., 2008). In addition, the hypoechoic areas of distortion seen with ILC on sonography have poorly defined margins, such that sonographic measurements can underestimate tumour size (Ferré et al., 2017; Ozcan et al., 2023; Vijayaraghavan et al., 2018). It is recognised in the literature that sonographic tumour size assessment is poorly correlated with final histology. This is seen in the cohort,

with greater measurement discrepancy noted with an increase in tumour size (Figure 3.14). This is consistent with findings in the literature (Gruber et al., 2013; Wang et al., 2014).

Tumour size estimation is more challenging for certain imaging findings. Characteristics such as architectural distortion or asymmetry are recognised as features that have ill-defined margins. In addition, measurement of a spiculated lesion can also be difficult as the tumour extent may be unclear (Cherel et al., 2005; Flanagan et al., 1996). Current practice is to exclude the spiculae from lesion measurement (Flanagan et al., 1996). This is the practice in our institution. In this study, the most common mammographic abnormalities associated with ILC were irregular ill defined masses, followed by architectural distortions, and then spiculated masses, a finding that is consistent with published literature (Chamming's et al., 2017; Durand et al., 2016; Johnson et al.; Lopez and Bassett., 2009; Tagliati et al., 2021; Yeap et al., 2018).

An interesting feature in this study, is that histology demonstrated the presence of microcalcification in only 10.68% of cases, a finding also commented on in the literature, with other reports noting that lobular cancer is rarely associated with calcification (Chamming's et al., 2017; Lopez & Bassett., 2009; Tagliati et al., 2021). Although the presence of extensive calcifications can improve tumour visibility on mammography, it can often result in overestimation of tumour size, especially on breast MRI in the presence of DCIS (Vijayaraghavan et al., 2018). The three cases with LCIS noted on preoperative biopsy and/or on final pathology resulted in size discrepancy with all imaging modalities. All the patients were from the screen detected cohort with architectural distortion and calcification noted on tomosynthesis. This finding may inform clinicians on the benefit of additional imaging in the presence of extensive calcification and allow for more detailed discussion with patients regarding choice of operation.

Breast density is a recognised risk factor for breast cancer, which is now incorporated into some breast cancer risk stratification models (Acciavatti et al., 2023; Edmonds et al., 2023). Mammographic density assessment with tomosynthesis has been standardised with the introduction of automated volumetric methods. Research has shown that subjective assessment of density can result in interobserver variability (Portnow et al., 2022). Studies have demonstrated an improvement in correlation when

compared with subjective assessments of breast density (Morrish et al., 2015). The Hologic Quantra software system was incorporated into tomosynthesis in the HDUHB in 2015, a method which has been shown to be reliable and reproducible, (Ekpo & McEntee., 2014; Gastouniotti et al., 2021; Wang et al., 2020). However, research has found that even these systems may estimate density less consistently in very dense breast tissue (Brandt et al., 2016).

The negative effect of breast density on tumour measurement is well recognised in the literature. Breast composition in this study found that two thirds of the cohort had fatty breast tissue (Category 1, 66.01%), with 39.89% in the very dense group (Category 2). This may not be representative of other populations with different demographics. The database was reanalysed by density group, with the results suggesting that discordance with size assessment with DBT is more pronounced in dense breast tissue. This is unsurprising as margin delineation can be more difficult in non-fatty breast tissue. These findings are consistent with previous studies that suggest that although tomosynthesis has improved imaging in dense breast tissue when compared with DM, imaging in very dense tissue (Category D) can still be challenging (Conant et al., 2019; Förnvik et al., 2018; Rafferty et al., 2016).

The effect of breast density on tumour measurement with tomosynthesis was explored for each density category. DBT measurements in the low breast density group, A and B (Category 1), showed improved correlation with pathology, Spearman's rank correlation results from this study, $r_s(64)=[.560]$, $p<.001$, compared with denser breast tissue readings in Category 2, $r_s[28]=[.371]$, $p=[.044]$ (Figure 3.8; Figure 3.9). These findings are consistent with previous studies that suggest that although tomosynthesis has improved imaging in dense breast tissue when compared with DM, imaging in very dense tissue can still be challenging (Conant et al., 2019; Rafferty et al., 2016). In addition, this study demonstrated the increasing negative effect of breast density on tumour size assessment when the 5mm tolerances were investigated. The agreement between tomosynthesis lesion size and final pathology reduced from 54.5% to 40%, and, additionally, the percentage of patients with underestimation of tumour size by 5mm doubled (Table 3.15). Included in this analysis, was a young patient with very dense breast tissue (D), who presented with breast pain. Tomosynthesis imaging demonstrated a few pleomorphic calcifications in the inner quadrant of the right breast,

with no other lesion seen. There was no abnormality on sonographic assessment. DBT guided VAB confirmed the presence of Grade 2 lobular cancer which was occult on tomosynthesis. The findings on MRI were of an enhancing area consistent with malignancy. The patient proceeded to mastectomy. The final pathology demonstrated widespread LCIS, with no invasive component. The histology from the VAB was reviewed and confirmed to be invasive, the primary invasive lobular component had been removed during the biopsy. This case was one of the significant outliers seen on all imaging modalities. This case highlights the difficulties with breast imaging in dense breast tissue which has been well documented in the literature (Conant et al., 2019; Rafferty et al., 2016).

These results illustrate how size assessment of lobular cancer by both tomosynthesis and sonography in this study, is associated with increasing discrepancy with pathological assessment, resulting in greater underestimation of disease extent, a finding that has been noted in the literature (Chudgar et al., 2017; Förnvik et al., 2018). Although tomosynthesis has improved cancer detection rates, lesion measurement in very dense breast tissue remains problematic, with the technology often underestimating the size of the lobular cancer (Fasching et al., 2006). This is seen in this study and is especially relevant in very dense breast tissue (Density D), as seen in Cohort numbers 47, 67 and 69, illustrated in Table 3-11. The results from this study are consistent with the literature demonstrating how density does not significantly affect tumour size measurement with MRI, with greater correlation between the MRI measurements and final pathology, than DBT and sonography for all density groups (Figure 3.23)

The analysis was repeated using age range. The error bar chart in Figure 3.20 shows that the mean tumour sizes tended to decline with increasing age of the patients, suggesting that tumour size was higher in the younger patient. This is consistent with the findings of studies assessing the effect of age on lobular cancer, noting that although the tumour is less common in the younger age group, the tumour size is often much larger compared with older women (Förnvik et al., 2010; Mariscotti et al., 2014; King et al., 2015; Ozcan et al., 2023). These studies also demonstrated how breast density affects tumour size assessment, especially with regard to the lobular subtype. Of the cohort under 50 years of age, 77.78% (7/9) had dense breast tissue (C6 + D1).

The breast density of the remaining 2 patients was Category B. The results in Figure 3.23 are consistent with those in the published literature assessing the effect of breast density on assessment of tumour size, suggesting that MRI is less affected than the standard breast imaging tools (Lowry et al., 2020; Marinovich et al., 2019).

An interesting observation from the study is the effect of breast density on sonographic measurements, suggesting that measurement of lobular cancers using breast ultrasound may also be limited in dense breast tissue. The correlation in this study reduced from $rs(60)=[.384], p=[.002]$, to $rs(19)=[.244], p=[.287]$, although on multilinear regression analysis after removal of outliers, this did not appear to be as evident. This may be a consequence of a small sample size ($n=21$) in the denser category. However, this has been recognised in the literature with studies demonstrating the inverse relationship between sonographic size and breast density, especially with increasing tumour size (Vijayaraghavan et al., 2018). Some studies have proposed the use of sonography in the assessment of patients with very dense breast tissue in a mammographically normal breast (Brem et al., 2015). This was recently investigated in the ASTOUND study. This prospective trial assessed the benefit of sonography in mammographically negative breasts and found that the addition of breast ultrasound almost doubled cancer detection rates (Tagliafico et al., 2018). This is especially pertinent as evidence now suggests that increased breast density observed on sonography should be considered a risk factor for breast cancer (Acciavatti et al., 2023; Edmonds et al., 2023). An interesting observation in this study is tomosynthesis measurements were more closely associated with sonographic than MRI assessment, especially in the dense breast cohort (Table 3.24).

Another finding from this study was the effect of tumour size on pathology discordance. Lesion measurement is challenging in large tumours, especially for cancers greater than 20mm, with studies finding that increasing size is associated with greater discordance with pathology (Marinovich et al., 2018; Vijayaraghavan et al., 2018). The effect of tumour size was assessed by separately evaluating tumour groups T1 (≤ 20 mm) and T2 (>20 to 49mm) for sonography, tomosynthesis and MRI. The results suggest that tumour size was underestimated in 58% of the T2 tumour group, but only in 5% of T1 cancers, while DBT overestimated lesion size in the T1 group in 27.5% of cases and 12.5% of the T2 tumours, suggesting a trend toward overestimating

if the index lesion was 20mm or less, and underestimation if the cancer was over 20mm. Similar findings have also been reported in the literature (Förnvik et al., 2010; Luparia et al., 2013; Şendur et al., 2021). The findings from this study suggest that the tomosynthesis and sonographic tumour measurements were more accurate in the lesions under 20mm, although MRI measurements were less influenced by tumour size, MRI assessment of smaller tumours was more accurate. Similar conclusions have also been reported in the literature (Förnvik et al., 2010; Luparia et al., 2013; Şendur et al., 2021), with some studies suggesting that MRI is also more accurate in T1 lesions (Hovis et al., 2021; Muttalib et al., 2014). Although there are some limitations in regard to overestimation of tumour extent, with a subsequent increase in mastectomy rates, the results from this investigation and published studies agree that MRI is currently the most accurate imaging modality for evaluating index lesion size and extent of disease (Gest et al., 2020; Mann et al., 2008; Rominger et al., 2016).

In breast cancer surgery, clear margins are an important therapeutic consideration, with current guidelines set at a minimum of 1mm for conservative breast surgery (Bundred et al., 2022). Assessing the DBT data with tolerances of within 5mm allowed a more clinically practice-based approach to margin assessment. This analysis is often seen in studies in the literature. The results suggest that for the whole cohort, tumour size was within 5mm in 48%, underestimated in 35% and overestimated in 13%. This was an interesting finding. The tolerances were then applied to the tumour size sets. With T1 tumours, the size agreement was within 5mm in 67.5% of cases, compared with 37.5% with T2 and T3 tumours. These findings suggest that with an increase in tumour size, there is a consequential increase in tomosynthesis/pathology size discrepancy.

Reviewing the evidence for standard imaging in the evaluation of lobular breast cancer, this study noted that in the presence of increasing breast density and tumour size, both sonography and tomosynthesis underestimate lesion measurement. The discrepancy can be partly due to the classical appearance of ILC on both mammography and ultrasound, with the tumour often appearing as a hypoechoic mass that can be difficult to measure (Ferré et al., 2017). Over two thirds (66.99%) of the cancers in this study were seen as a mass with irregular and ill-defined margins. Another imaging feature that was seen in this study is architectural distortion, a feature which can also be difficult to assess. Studies note that size correlation with final

histology in the presence of a distortion, can be limited especially on sonography, with size discrepancies of up to 77% quoted in some studies (Garlaschi et al., 2019). Distortion was seen in 32.04% of sonographic assessments in this study, and as noted in the literature, sonographic measurement of these image findings is inherently difficult (Munot et al., 2002; Wong et al., 2018). Although, some studies have documented good sensitivity rates of identification of ILC with sonography of up to 83% (Molland, et al., 2004), there is general agreement in the literature that size assessment is often underestimated with this imaging modality (Ferré et al., 2017; Ozcan et al., 2023; Vijayaraghavan et al., 2018).

MRI imaging has high sensitivity for cancer detection which is largely independent of breast density (Mann., 2010; Muttalib et al., 2014; Parvaiz et al., 2016). Findings which are consistent with published literature (Leddy et al., 2016; Lowry et al., 2020; Marinovich et al., 2019). Although these results suggest that preoperative ILC size assessment is best assessed with MRI, patients with fatty breasts (Category 1/A) could potentially be stratified into a group that may not require additional imaging with MRI, a finding that is consistent with the published literature (Chudgar et al., 2017; Förnvik et al., 2018). However, further investigation into preoperative size assessment that may establish new guidelines would require a prospective, decision impact study with a large enough sample size to ensure validity.

The ongoing quest for improved surgical outcomes for patients with early breast cancer continues. This is partly dependent on imaging. The conclusion of this study is that tomosynthesis is not a substitute for MRI in the evaluation of lobular breast cancer, as the latter provides a more accurate and precise estimate of tumour size. This is consistent with published research comparing the diagnostic performance of MRI and DBT in all tumour groups and in lobular cohorts, where preoperative size assessment with MRI shows a stronger correlation and size agreement with final pathology (Förnvik et al., 2010; Förnvik et al., 2018; Luparia et al., 2013; Muttalib et al., 2014). The opportunities offered by the application of AI to existing techniques, may well herald an era of technological improvements that enhance surgical outcomes.

3.5.4 Limitations

The project was initially conceptualised as a prospective study. Time constraints and practical issues precluded this. Consequently, a non-randomised retrospective single institution study was performed introducing the possibility of selection bias. Other potential limitations are listed below.

3.5.4.1 Cohort Characteristics

The study population in Southwest Wales is homogeneous and not racially diverse. ONS figures collated in 2021 (<https://www.ons.gov.uk/census> accessed 21/07/2023) found that 97% of the population in Carmarthenshire are predominantly White and the percentage of women over 30 years of age is 35.89%. Therefore, the findings of this study may not apply to more diverse populations. The cohort consisted of screening and symptomatic patients which may also have contributed to bias in the final results, as tumours in the screening population tend to be smaller, and the age range of the individual is predefined, typically 50 to 70 years. Missing images, most notably in the sonographic cohort, reduced the number of patients with all 3 imaging modalities to 78. This sample size is consistent with many studies in the published literature.

3.5.4.2 Reader Variability

Inter- and intra-observer variation in imaging has been well documented in the literature (Berg, et al., 2000; Kopans, et al., 2008; Skaane, et al., 2008). Both readers have worked in the breast service for over 25 years, and although their working practice is similar, it is inevitable that interobserver and intraobserver errors may have influenced the results. This could have been improved if the readers re-reported all the anonymised films on two separate occasions, which may have increased the validity of the results. The interval between the reading sessions would have had to be sufficient to minimise recall bias. The reading station system is programmed to remove images that are read such that space is created to accept newer images. This would have been impractical as resources and time were limited. Sonographic images were retrieved from PACS. These assessments are made in real-time. The measurements were taken from the captured image measurements. This introduced the potential of interobserver difference. Although many were reported by reader 2, there were a significant number that were seen by other clinicians from the screening service. MRI

measurements and reports were provided by Reader 1. The study followed standard clinical practice, with images reported in view of the tomosynthesis findings, which may be a confounding factor.

3.5.4.3 Internal and Construct Validity

To improve internal validity, a mix of ductal and lobular images sets were considered. However, this was not possible owing to logistics. To reduce the effect of construct validity, the readers met to discuss mammographic lesion measurement. Review of practice suggested that mono-operation bias was small in most cases. Re-reading the original data set was considered to ascertain whether the measurements were the same, and to evaluate intraobserver bias. This was not possible owing to time and financial constraints.

3.5.4.4 Pathology

During the period of investigation, there were some changes to the pathology staff in PPH, with breast histology reported by three separate pathologists, introducing a potential risk of inter-observer bias and intra-observer bias in the reporting of tumour size.

3.5.4.5 Synthetic 2D

The original proposal for the study was to evaluate size measurement on s2D. However, this proved to be impractical and inconsistent with standard practice. Following the preliminary meeting to discuss trial procedure it was felt that this should be abandoned. The issues with measurement with s2D that were experienced by myself and AM have subsequently been noted in the literature (Şendur, et al., 2021).

3.6 CONCLUSION

The use of tomosynthesis in the preoperative assessment of patients with ILC demonstrates moderate correlation with final pathology size in patients with breast density A and B, and with tumour sizes less than 2cm. This study suggests that a prospective randomised controlled trial assessing CESM without the addition of MRI

in selected patients may be helpful in stratifying imaging for staging early lobular breast cancer.

Breast medicine requires a nuanced approach for each individual case within the context of protocols and guidelines. Final decisions need to be personalised for each patient. ILC is a special type of breast cancer that needs this type of dedicated approach. Advances in artificial intelligence (AI) with additional platforms such as contrast-enhanced mammography, and the incorporation of molecular assays into MRI techniques. may herald a new era of imaging that improves diagnosis and assessment all types of breast cancer, including lobular cancers.

CHAPTER 4: SYSTEMIC INFLAMMATORY INDICES

4.1 INTRODUCTION

Survival rates for breast cancer in the UK (Taylor et al., 2023) and developed countries continue to improve (Arnold et al., 2022). This has been largely attributed to screening, improved imaging and surgical techniques, along with advances in chemotherapy regimens with targeted therapies. Following surgery, decisions surrounding treatment in the postoperative setting to reduce the risk of recurrence, are largely based on clinicopathological factors such as histological grade, tumour size and nodal status. In addition, *HER2* expression and hormone receptor status are important considerations when evaluating the benefit of chemotherapy and adjuvant hormonal therapy. It is widely accepted that chemotherapy with targeted therapy is indicated in *HER2* positive breast cancer. Also, for tumours that do not express *HER2* or hormone receptors (TNBC), the use of chemotherapy has been shown to improve long term outcomes (Han et al., 2023). However, most breast malignancies express *ER* and progesterone receptors *PR*, with approximately 70 to 80% of all breast cancers being *ER* positive (Early Breast Cancer Trialists Collaborative Group et al., 2011). Although these receptors are targets for treatment, as they predict a response to anti-oestrogen therapy (EBCTCG., 2005), the benefit of adjuvant chemotherapy in these cases is variable. This can be partly explained by the degree of heterogeneity within tumours that are hormone receptor positive (Cancer Genome Atlas Network., 2012; Paik et al., 2006; Perou et al., 2000).

Following on from the seminal work by Perou et al (2000) and others, the molecular classification of breast cancer is now generally divided into four main subtypes; Luminal A, Luminal B, *HER2* and Basal type (see Section 1.7.1). The aim of the subgroup classification system is to enhance the stratification of breast cancer, thereby informing treatment decisions to improve long term outcomes (Prat et al, 2015). This personalised approach has been developed further with the widespread use of genomic testing in *ER* positive early breast cancer, providing additional information which identifies patients at an increased risk of relapse, and additionally, cases that may benefit from adjuvant chemotherapy.

4.1.1 Luminal Subtype

Luminal subtypes are the most common cancers, comprising up to 80% of all breast malignancies (Ciriello et al., 2012; Harbeck et al., 2019). Interestingly, genomic studies have noted a higher degree of heterogeneity within this subgroup compared with other subgroups (Cancer Genome Atlas network, 2012; Ciriello et al., 2013). Most lobular breast cancers are classified as luminal A (Iorfida et al., 2012), with 80 to 90% *ER* positivity in ILC noted in the literature (Arpino et al., 2008; Oesterreich et al., 2022; Rakha et al., 2008) (Section 1.2.2). However, some lobular variants, such as the pleomorphic subtype, have lower *ER* positivity, with a small percentage of these tumours being TNBC or overexpressing *HER2* (Rakha & Ellis, 2010).

It is recognised that despite adjuvant therapy, luminal A tumours have a propensity to relapse many years after the original diagnosis and surgery (Blows et al., 2010; Haque et al., 2012; Pan et al., 2017; Prat et al., 2015). A large meta-analysis of nearly 63,000 patients found that tumour size, nodal status and grade were strong predictors of late recurrences (Pan et al., 2017). This appears to be especially true for lobular breast cancers (Colleoni et al., 2012; Cristofanelli et al., 2005; Esserman et al., 2011; Iorfida et al., 2012), suggesting that a more tailored approach for lobular tumours may be required.

Traditionally, decisions surrounding systemic therapy in lobular breast cancer have been made on the clinicopathological features of the tumour, such as tumour grade and size, in addition to the axillary nodal status; TNM staging (Section 1.3.4). Furthermore, the oestrogen receptor is a target for treatment in luminal breast cancer, with adjuvant endocrine therapy prescribed to most individuals with *ER* positive disease, with studies demonstrating a benefit in survival (EBCTCG, 2011). This is especially relevant in lobular tumours, with 80-90% *ER* positivity (Colleoni et al., 2012). However, the use of chemotherapy in ILC has been more reserved, as early studies suggested that this type of breast cancer was less chemosensitive when compared with IDC, especially in the neoadjuvant setting (Cristofanilli et al., 2005; Katz et al., 2007; Marmor et al., 2017; Thomas et al., 2019). A number of these studies were retrospective, and, as such may have been underpowered to reliably demonstrate a benefit to chemotherapy. Additionally, the lobular cohort outcomes were often evaluated by subgroup analysis, which may have resulted in false negative findings,

suggesting that this subtype was less sensitive to chemotherapy. However, it is generally acknowledged that lobular breast cancers demonstrate poorer response to chemotherapy when compared with ductal tumours. This is most likely related to the biology of lobular breast cancers, with high expression of *ER*, low *Ki-67* level, and moderate to low histological grade (Sledge et al., 2016). Although, subtypes of ILC, such as *HER2* positive pleomorphic ILC and triple negative receptor lobular cancer, do benefit from neoadjuvant and adjuvant chemotherapy.

It is evident from population studies that demonstrate a higher rate of late recurrence in lobular cancers when compared with IDC (Oesterreich et al., 2022; Pestalozzi et al., 2008; Rakha et al., 2008), that a tailored approach to neoadjuvant and adjuvant therapy in this subgroup may be needed. Patients with ILC often develop late recurrences, with metastatic spread to anatomical sites that are unique to this type of breast cancer (Arpino et al., 2004; Inoue et al., 2017; Korhonen et al., 2013; Pestalozzi et al., 2008), (Section 1.3.5). There is ongoing interest in the breast research community regarding optimising adjuvant therapy in lobular cancers, as some prognostic models may not accurately reflect recurrence risk in this subtype.

4.1.2 Prognostic models

The use of prognostic models can help stratify patients with early breast cancer, thereby facilitating treatment and management decisions. A well-established, internationally recognised and validated prognostic tool is the NPI (Blamey et al., 2010; Haybittle et al, 1989; Kerin et al., 2022). The index is calculated on clinicopathological factors, tumour size in centimetres, grade (1 to 3), and lymph node status (1 to 3 point scale) (Table 1.4; Section 1.7.3). A recent systematic review and meta-analysis of 19 studies evaluating the association between five and ten year survival and NPI, found significant differences in the survival estimates, raising concerns about the functionality of the test as a prognostic tool (Gray et al., 2018). However, the studies included in the review were heterogeneous regarding the populations investigated, and additionally, the number of NPI categories used in the analysis. For example, one study in Wales investigating five and ten year survival for women screened over a 4 year period, found that the NPI was predictive in this cohort

of 1,546 women (Fong et al., 2015). There were four NPI groups in this study, whereas other researchers have used the standard three categories, as in this current project. This heterogeneity was noted as a confounding factor in a more recent systematic review of prognostic models (Phung et al., 2019). The authors concluded that the NPI predicted prognosis in most populations, however in cases with high risk histology, and in patients at the extremes of the age scale (young and very old), the model performed less well (Engelhardt et al., 2013; Phung et al., 2019). These limiting factors were also found with the other models evaluated in this systematic review, with prognostication with *Adjuvant!* Online (Section 1.7.4.1) and PREDICT v1.3 (Section 1.7.4.2) demonstrating inconsistent results (Engelhardt et al., 2017; Wishart et al., 2011). However, despite attempts to improve prognostication, studies suggest that clinicopathological factors, such as nodal status, tumour grade and size, are still relevant (Phung et al., 2019). Similar findings were noted in a retrospective, single centre analysis of 1471 patients, where 12% (n=176) of the cohort had ILC, the study found that the NPI provided relevant prognostic information (Kerin et al., 2022). Of note, the authors compared prognostication with NPI against Oncotype DX® RS testing, and concluded that neither test predicted survival outcomes, although the former was superior at predicting DFS and OS (Kerin et al., 2022).

Prognostication in lobular cancer with NPI has been investigated, with results suggesting that although histological grade remains an important independent risk factor, as the majority of lobular cancers are Grade 1 or 2, with only 10% Grade 3 (Engstrøm et al., 2015; Iorfida et al., 2012; Rakha et al., 2008), the utility of this index may be limited in this subtype. Additionally, most ILC's are T1 or T2 in size, such that the NPI of most node negative ILC is in the good to moderate category, potentially failing to identify tumours with a poorer prognosis (Rakha et al., 2008). These issues are compounded as lobular cancers can be difficult to accurately grade, as pathological features, such as tubule formation, nuclear pleomorphism and atypia, and mitotic count, are fairly uniform in classical ILC (Oesterreich et al., 2022). The emergence of molecular signature-based tests, which aim to reflect the unique morphomolecular and histological characteristics of breast cancer, suggested that this may herald an era of improved prognostication for patients with lobular malignancies.

Genomic testing has become firmly established as one of the tools used to assess the benefit of adjuvant chemotherapy in the management of hormone receptor positive early breast cancer. Prognostic multigene assays are modelled on molecular signalling pathways and genetic signatures, with the aim of reflecting the true heterogeneity of breast cancer more accurately. Evidence from large prospective trials in all breast cancer subgroups, has confirmed both the prognostic and predictive ability of these tests. One of the most widely used tests is the 21-gene assay, Oncotype DX® Recurrence Score (RS), which is validated as both a predictive and prognostic tool in node negative hormone receptor positive early breast cancer (Section 1.7.5.1). The expression of 16 tumour related genes and 5 control genes is measured, and a RS calculated algorithmically. The results range from 0 to 100, initial studies stratified patients into three groups: high (≥ 31), intermediate (18-30), or low risk (< 18), with the former receiving the greatest benefit from chemotherapy. The cut-off levels have since been modified in the over 50 age group, with a score of greater than 25 indicating a benefit from chemotherapy (Sparano et al., 2018). In addition, the RS cut-off for low risk in women under 50 years of age, is now 16.

The use of Oncotype DX® RS is accepted practice in many countries and is included in international guidelines as an assessment tool for adjuvant treatment choice in early breast cancer (Harris et al., 2007; Ross et al., 2008; Ward et al., 2013). However, there are limitations associated with the test; namely cost, borderline results, and possible treatment delays waiting for the result, such that less expensive methods of prediction and prognostication would be welcome. In addition, as outlined in Section 1.7.5.1, Oncotype DX® RS may not accurately reflect prediction and prognostication in lobular breast cohorts, and, in addition, testing often produces intermediate risk scores in ILC which can be challenging to manage (Christgen et al., 2020; Conlon et al., 2015; Tsai et al., 2016).

To compound the issues related to prognostication and prediction in lobular cancer, when compared with other subtypes, the Oncotype DX® RS is rarely high, with percentages of high RS score of 0.5 to 8 quoted in the literature (Christgen et al., 2020; Kizy et al., 2017; Tadros et al., 2018). This can be partly explained by the relatively low proliferation rate seen in lobular cancers which typically demonstrate high *ER* positivity and low *Ki-67* levels, such that the RS may underestimate the benefit of

chemotherapy in this group of patients. In addition, the lobular subgroup, is further divided into a number of variants with different prognostic outcomes. These factors have been shown to result in issues regarding accurate reporting of lobular breast cancer histology. This was seen in the pathological review of lobular cancers in the MINDACT trial. In this subanalysis, the pathology of all the lobular cancers entered into the trial were centrally reviewed by an experienced pathologist. This pathological review confirmed that only 60% of cases assigned ILC were lobular breast cancers (De Schepper et al., 2022). These findings have also been noted in another large study, in which, only 66% of ILC cases entered into the trial were confirmed as lobular cancers (Christgen et al., 2020). Although, lobular subtypes of breast cancer such as the classic type are considered low risk, in the MINDACT trial 10% of Classic ILC had high risk scores, with most tumours being low or moderate risk (90%), and analysis of the risk scores of the pleomorphic variant confirmed that 23% were high risk, with 76% demonstrating low risk scores (De Schepper et al., 2022). These discrepancies highlight the need to consider whether alternative tests may provide improved prognostication in lobular cohorts.

With studies in the literature evaluating the use of systemic inflammatory indices in solid tumours suggesting that these parameters may be predictive of outcomes, the utility of these ratios was considered in breast cancer prognostication. The tests are based on evidence on the role of inflammation in tumour development and progression, which has been well documented (Jiang & Shapiro., 2014). Systemic inflammatory markers, assessed from peripheral blood samples, have been evaluated as potential prognostic and predictive markers in solid tumours with promising results seen in certain tumour groups (Proctor et al., 2012), such that the systemic inflammatory indices may have potential as a surrogate test to Oncotype DX® RS in selected patients with early breast cancer.

Most research has evaluated the utility of the Neutrophil-to-Lymphocyte Ratio (NLR), the Platelet-to-Lymphocyte ratio (PLR), the Monocyte-to-Lymphocyte Ratio (MLR) and a combination of the NLR and platelet level in a Systemic Inflammation Index (SII = NLR x Platelet level). Two meta-analyses suggested that the NLR has potential as a prognostic marker for breast cancer (Guo et al., 2019; Wei et al., 2016), with findings in the literature demonstrating promising results in a variety of other solid

malignancies (Chen et al., 2018; Giakoustidis et al., 2018). These ratios are readily available as they can be calculated from the preoperative blood results and, as such, may provide a potentially inexpensive alternative to the commercial multigene assays. However, many of the studies evaluating the use of these indices in breast cancer have not differentiated between intrinsic breast cancer subtypes and, additionally, have used different cut-off levels for normality.

A meta-analysis by Guo and colleagues (2019), found the NLR and PLR to be prognostic in a subgroup analysis of *HER2* positive patients. This was also the conclusion of the GEICAM/9906 study analysing the prognostic role of the NLR in early breast cancer (Templeton et al., 2018), where a non-significant association was detected between elevated NLR and non-luminal subtypes. Other studies have also investigated the utility of systemic inflammatory indices, especially in triple negative breast cancers and found that the indices were prognostic (Asano et al., 2018; Ji & Wang., 2020). However, one single centre retrospective analysis of 442 patients with all breast cancer subtypes in Korea, suggested that the NLR was only prognostic in the luminal A subtype (Noh et al., 2013). To date, studies assessing the use of the systemic inflammatory indices in lobular breast cancer have yet to be published.

4.2 AIMS

The aim of the study is to investigate the correlation between the systemic inflammatory indices SII, NLR, PLR, MLR, the NPI and the Oncotype DX® RS in node-negative early breast cancer, to ascertain whether any of the ratios have potential as predictive and prognostic tools for use in the adjuvant setting in selected groups of patients, such as pre/postmenopausal women, and those with ILC or IDC. The lobular cohort was analysed separately. Clinicopathological features were investigated to evaluate risk.

4.3 MATERIALS AND METHODS

A single centre retrospective study was undertaken following local and UK ethical approval. The unit commenced Oncotype DX® RS testing from 2007, with results from three district general hospitals within the Hywel Dda University Health Board surgical oncology units held on one database. Oncotype DX® RS testing is performed on unstained slides of formalin-fixed paraffin-embedded tissue as per the manufacturer's guidelines.

Currently decisions regarding the use of Oncotype DX® RS testing are made in the multidisciplinary Hywel Dda weekly breast meeting. Patients with moderate risk histology based on tumour size over 2cm, are offered recurrence score testing if they are suitable for, and would consider, adjuvant chemotherapy if indicated. Prior to this date, testing was offered on a more general basis, with low risk and smaller tumour size histology also considered.

4.3.1 Cohort

Patients treated for early breast cancer with post-surgical Oncotype DX® RS testing between 2007 and 2020 were identified and given unique identification numbers (n=607). Some of these individuals had been included in a decision impact and economic evaluation study in Southwest Wales (Holt et al., 2013). The Oncotype DX® RS was recorded in the database. RS levels were grouped into two categories, high and low risk, with high risk > 25 in patients over 50, and >18 in under 50 years of age. These levels are considered working cut-offs for consideration of chemotherapy benefit in the UK following data from the TAILORx (Sparano et al., 2018), and RxPONDER trials (Kalinsky et al., 2021). Of note, the RS level for consideration of chemotherapy in the under 50 age group has been updated and is now set at a score over 16.

A review of clinical records was undertaken to ascertain the date of diagnosis, age at diagnosis, comorbidities, smoking status, medication at diagnosis, family history (including BRCA carriers), date last seen (follow-up period), date and types of recurrence, date of death and cause of death. Primary care records were accessed for

cause of death if this was not recorded on the central system. Confirmation of receipt of chemotherapy was also obtained from the records.

4.3.2 Nottingham Prognostic Index

Pathology reports of the cohort were retrieved. Operative details with date of procedure were noted. Tumour characteristics recorded included size, grade, lymph node status, ER and PR levels. In addition, presence of DCIS or LCIS was noted. The NPI was calculated for all patients using the formula: $NPI = \text{tumour size (in cm)} \times 0.2 + \text{Tumour Grade (1-3)} + \text{lymph node status (1=negative, 2= one to three nodes positive, 3 = greater than three nodes positive)}$. The groups were classified into 3 categories (consistent with the literature): Good ≤ 3.4 , Moderate $>3.4 - 5.4$, Poor > 5.4 (Gray et al., 2018).

4.3.3 Oncotype DX RS

Decisions surrounding the use of Oncotype DX® RS testing are made in the HDUHB joint Breast MDT. Individual cases are discussed with the results of the final pathology. If the histological parameters suggest that testing will improve prognostication the case is considered for assessment. This is with the proviso that the patient considered for RS testing is fit and willing to have chemotherapy should the result suggest that this would benefit outcome. Patients are counselled prior to requesting a test.

Oncotype DX® RS results for all patients were obtained from the patient and unit-held records from 2007 to 2017, and from online results between 2017 to 2020. Exclusion criteria included Oncotype DX® RS for preinvasive histology (Ductal Carcinoma in-situ (DCIS)), pure mucinous histology (mixed ductal or ductal with mucinous features, or mixed ductal/lobular histology were included in the ductal cohort), axillary node positivity and subjects lost to follow-up. Patients with no preoperative peripheral blood analysis were also excluded. All patients included in the study were female.

4.3.4 Systemic Inflammatory Indices

The preoperative Full Blood Count (FBC) result was recorded from the clinical records and used to calculate the NLR, MLR, PLR and SII for each patient in the cohort. The SII was calculated using the formula Neutrophil Count x Platelet count/Lymphocyte count ($N \times P/L$). The cut-off levels were chosen following a review of the literature. Recent population based prospective cohort studies suggest reference levels for the most frequently referenced inflammatory markers, where a 97.5% limit of normal was used as a cut-off between normal and elevated: NLR=3.53, PLR=246, MLR=0.47, SII=1169 (Fest et al., 2018; Forget et al., 2017).

4.3.5 Statistical Analysis

Data analysis was performed to assess clinicopathological features, outcomes, and features of the total cohort, with special reference to the lobular group of patients. Descriptive analysis was performed on the dataset by age and tumour type (lobular and ductal). Statistical linear regression analysis was performed with Pearson correlation and Spearman's rho correlation calculated for both tumour subtypes.

Statistical analysis of the lobular cohort was also performed to ensure robust analysis of the data as directed by the IRAS committee. The two accepted measures of non-parametric rank correlation are Kendall's tau and Spearman's (rho) rank correlation coefficient. These analyses were used to measure the strength of the relationship between the variables. The dataset was analysed as a whole and then for each subtype, and for both age groups, evaluating the correlation between RS and both SII and NLR. The reason for choosing the two tests is that Kendall's Tau rank correlation is insensitive to error, so the resultant *p*-values are more accurate with smaller sample sizes, whereas Spearman's rho is more suited to larger sample sizes, the results are more sensitive to error and discrepancies in the data. Dr G. R. Davies (G.R.D), given his experience in using the software, performed the processing of the statistical analysis in Stata/IC v16, operating in a Windows environment. The data were then analysed to assess correlation between the NPI, Oncotype DX® RS and the inflammatory indices calculated for each individual patient. Kaplan-Meier survival

analysis was performed to look at each prognostic indicator without adjustment using published cut points, as discussed in section 4.3.4.

4.4 RESULTS

4.4.1 Cohort Characteristics

Oncotype DX® RS testing was requested on 602 patients within the 13 year study period. Exclusions included 68 node positive patients, 3 Tubular carcinomas, 6 Mucinous Carcinomas, 1 Medullary Carcinoma, 6 pure DCIS patients, 13 patients lost to follow up, and 10 patients with no peripheral blood testing preoperatively. The final cohort consisted of 495 individuals: 395 (79.8%) IDC, 100 (20.2%) patients with ILC (Figure 4.1).

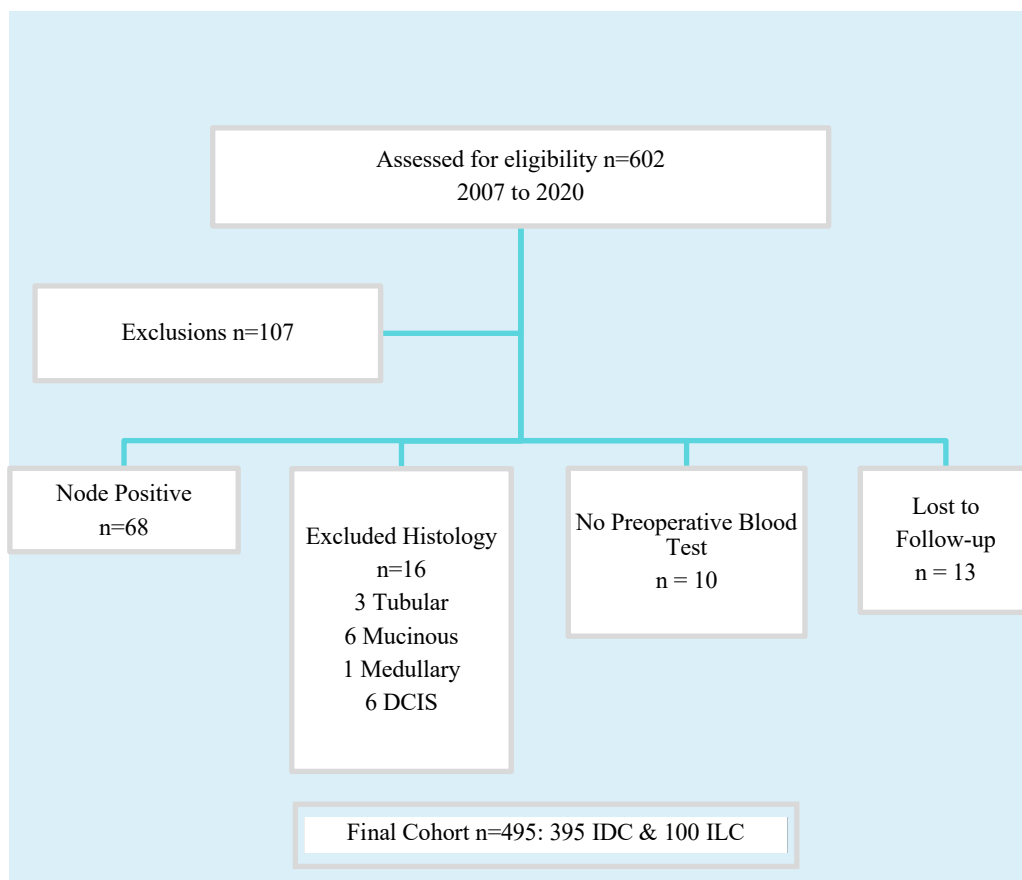


Figure 4.1 Systemic Inflammatory Indices Study Cohort Characteristics

The exclusion of node positive patients potentially skewed the balance of ductal to lobular cancer in the cohort. The number of patients with axillary nodal disease was significantly higher in the ductal patients who underwent Oncotype DX® RS testing, such that, in the cohort under investigation, the percentage of patients with lobular cancer was higher than in the general population (20.2%), compared with an incidence of 10 to 15% in the literature, potentially introducing bias into the analysis.

4.4.2 Clinicopathological Features

The mean patient age of the total cohort at diagnosis was 59 years (range 28 to 82). This is consistent with clinical practice and the literature. Breast cancer incidence in the UK peaks between 40 and 65 years of age. The mean invasive tumour size of the whole cohort was 23.2mm (range 2mm (IDC) to 120mm (ILC)). All tumours were oestrogen receptor (*ER*) positive (3/8 to 8/8), and Human Epidermal Receptor Growth Factor 2 (*HER2*) negative by immunohistochemistry (IHC). Most tumours were *PR* positive (86.67%). The percentage of *PR* negative cases, by both IHC and Oncotype DX® RS in each histology group, was 12.66% (50/395) IDC, and 16% (16/100) ILC.

The data was analysed according to standard working practice, with over and under 50 years of age analysed separately.

4.4.2.1 Patients Over 50 Years of Age

The management of patients is based on several clinical factors. Age is taken into consideration when assessing the risk of recurrence, and, in addition, the use of Oncotype DX® RS. The nationally and internationally accepted RS level for consideration of chemotherapy in the over 50 years of age cohort, is over 25.

The mean age of this group of patients was 62.76 years in the ductal tumour group and 63.84 in the lobular cohort (Table 4.1).

In addition, research has shown that tumour size is larger at presentation in patients with lobular compared with ductal cancer. The mean tumour size in the ductal cohort of patients was 21.2 mm (2 - 70mm), compared with the lobular group of patients with a mean of 31.4mm (7-120mm). This partly explains the higher mastectomy rate of the

patients with lobular cancer compared with the IDC group, with two thirds of the lobular patients in the over 50 age group undergoing a mastectomy, compared with only 20% in the IDC group (Table 4.1).

Evaluating the pathology of the tumours in the cohort confirm that 91.01% of the lobular cancers in the over 50 age group were Grade 2, compared with 61.83% in the ductal group.

The NPI category in the over 50 age group warrants discussion. The number of patients in the intermediate group in the ILC cohort suggests that Oncotype DX® RS testing was considered in the MDT when the clinicopathological findings were estimated as moderate risk. However, when the low and moderate risk NPI scores are combined, the groups are similar, with 98.74% of the IDC and 97.78% ILC within these prognostic levels. The systemic inflammatory indices datasets were similar for both tumour types.

Table 4-1 Clinicopathological features of patients 50 years and over

| N=406 | | IDC n=317 | ILC n=89 |
|----------------------------|----------------------|---------------------------|---------------------------|
| Mean patient Age (years) | | 62.76 (50 – 82) | 63.84 (50 – 78) |
| Mean Tumour Size (mm) | | 21.2 (2 – 70) | 31.4 (7.0 – 120) |
| Operative Details n (%) | Mastectomy | 65 (20.5) | 53 (59.55) |
| | Conservative Surgery | 252 (79.50) | 36 (40.45) |
| Tumour Grade n (%): | | | |
| I | | 53 (16.72%) | 4 (4.49%) |
| II | | 196 (61.83%) | 81 (91.01%) |
| III | | 68 (21.45%) | 4 (4.49%) |
| Mean NPI Score | | 3.67 (2.10 - 5.70) | 3.82 (2.49 - 6.6) |
| NPI Category: | Good <3.4 | 99 (31.23%) | 10 (11.26) |
| | Moderate 3.5-5.4 | 214 (67.51%) | 77 (86.52%) |
| | Poor >5.4 | 4 (1.26%) | 2 (2.25%) |
| Mean SHI | | 801.99 (115.86 – 5019.60) | 782.22 (262.28 – 2777.25) |
| Mean NLR | | 2.84 (SD 1.65) | 2.95 (SD 1.59) |
| Mean PLR | | 157.20 (SD 65.26) | 151.26 (SD 60.57) |
| Mean MLR | | 0.26 (SD 0.19) | 0.27 (SD 0.12) |

4.4.2.2 Patients under 50 Years of Age

In the under 50 age group, the mean age and tumour size was higher in the lobular cohort (Table 4.2). The rate of mastectomy was considerably higher in the ILC group,

with 9 of the 11 (81.82%) having a mastectomy, compared with 15 of the 78 (19.23%) of the patients with ductal cancer. The group had larger mean tumour sizes (28.5mm), compared with IDC patients (21.5mm) which may explain some of the difference in surgical outcomes, although the small number of patients (n=11) may have resulted in an overestimation of the mastectomy rate in the lobular cohort.

Investigation of the distribution of grade in the lobular cohort, confirms that in the under 50 year old group of patients, there were no Grade 1 tumours, with most cases being Grade 2 cancers (81.82%; n=9). The remaining 2 lobular tumours were classified as Grade 3, one of these being pleomorphic.

The NPI scores differ between the subtypes, with a higher mean NPI in the lobular cohort. This is not surprising given that the mean tumour size is higher in the ILC cohort, and the NPI formula incorporates grade and size of tumours. As over 80% of the lobular cancers were Grade 2, and larger in size than the ductal cohort, one would expect this as there were no node positive tumours included (the third NPI factor). Thus, the difference between the two groups is essentially size and grade. However, there were no ILC cases with high NPI scores, with only one patient with a high score in the ductal cohort.

Review of the inflammatory indices in this group of patients, confirms that although the ratios were slightly elevated in the lobular cohort when compared with the ductal, all the indices fell within normal limits.

Table 4-2 Clinicopathological features of patients under 50 years of age

| N=89 | | IDC n=78 | ILC n=11 |
|---------------------------------|-------------------------|---------------------------|----------------------------|
| Mean patient Age (years) | | 42.45 (28 to 49) | 44.27 (38 to 49) |
| Mean Tumour Size (mm) | | 21.3 (7 - 45.0) | 28.5 (12 - 60) |
| Operative Details: n(%) | Mastectomy | 15 (19.23%) | 9 (81.82%) |
| | Conservative surgery | 63 (80.77%) | 2 (18.18%) |
| Tumour Grade n (%): | | | |
| I | | 15 (19.23%) | |
| II | | 50 (64.10%) | 9 (81.82%) |
| III | | 13 (16.67%) | 2 (18.18%) |
| Mean NPI Score | | 3.48 (2.14 to 5.7) | 3.74 (3.30 to 4.56) |
| NPI Category: | Good <3.4 | 51 (65.38%) | 1 (9.09%) |
| | Moderate 3.4-5.4 | 26 (33.33%) | 9 (81.82%) |
| | Poor >5.4 | 1 (3.46%) | |
| Mean SII | | 832.09 (185.88 – 2597.70) | 966.89 (219.06 to 2882.39) |
| Mean NLR | | 3.12 (SD 1.83) | 3.20 (SD 1.72) |
| Mean PLR | | 147.41 (SD 49.45) | 167.72 (SD 52.70) |
| Mean MLR | | 0.29 (SD 0.42) | 0.25 (SD 0.12) |

4.4.2.3 Cohort Outcome Data

Survival data for the cohort was calculated (Table 4.3; Figure 4.2). The results are consistent with the literature, with a higher rate of late relapse in the lobular cohort, and worse outcomes compared with the ductal group especially between 5 and 10 years (Figure 4.2). There were very few deaths in the database cohort (n=13).

The lobular cohort outcomes are explored in greater detail in Section 4.4.7.3.

Table 4-3 Kaplan-Meier Survival Data

| Ductal (95% CI) | Lobular (95% CI) |
|-----------------------------|-----------------------------|
| 2 year 99.4 (97.4 to 99.8) | 2 year 98.7% (90.0 to 99.8) |
| 5 year 94.4 (90.2 to 96.8) | 5 year 96.8% (87.4 to 99.2) |
| 10 year 91.6 (86.0 to 95.1) | 10 year 84.6 (64.7 to 93.8) |

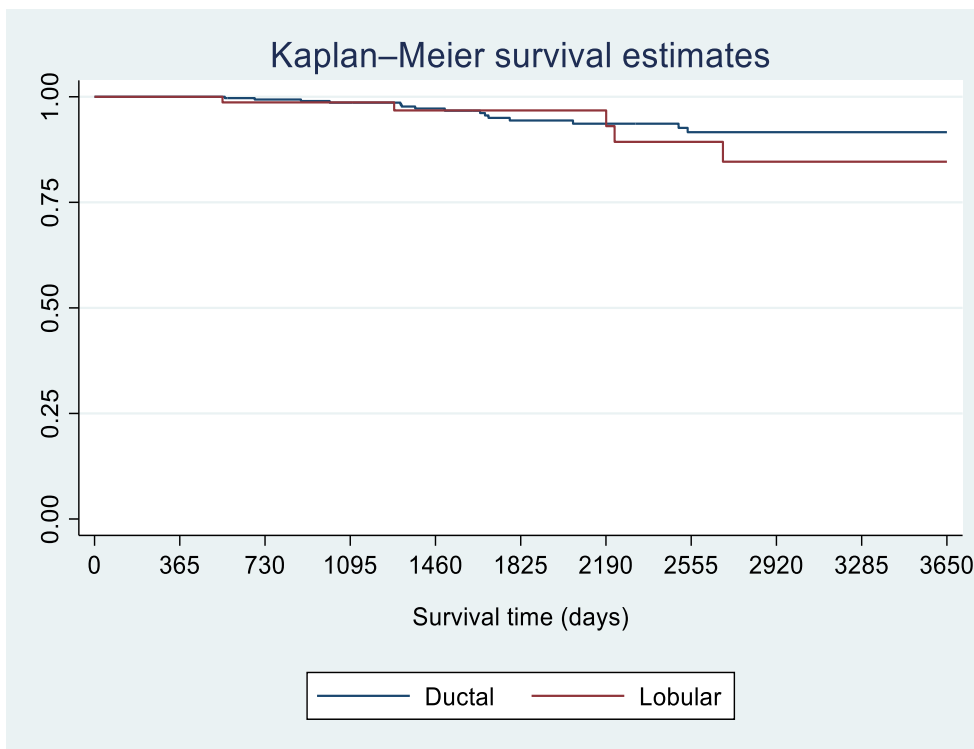


Figure 4.2 Kaplan-Meier survival estimate

Note: Kaplan-Meier survival estimates for cohort; ductal (Blue line) and lobular (Red line)

4.4.3 Oncotype DX® Recurrence Score Analysis

The results of Oncotype DX® RS testing for the whole cohort (IDC n=395; ILC n=100) were analysed (Table 4.4). The mean RS was lower in the lobular cohort (16.53) compared with the IDC group of patients (18.88). This is consistent with clinical practice and the literature. Most recurrence scores in the ILC cohort were of low or intermediate risk (RS<25), with only 6% of this group having a high score. However, 16.46% of the ductal group had a high Oncotype DX® RS, which may reflect the cohort of patients studied, as only 6% of the lobular tumours were Grade 3, compared with 14.6% of the ductal cohort.

Tumour sizes were also different between the histological types, with 13% of the ILC group having T3 cancers, compared with 0.76% in the ductal cohort. This partly explains the NPI differences seen within the two groups, although the percentage of patients in the high risk NPI category is similar. The mean NPI for the lobular cohort was 3.81(SD = .558) compared with 3.63 (SD=.701) for ductal cancers. This is related

to the grade of the tumours, with a smaller number of high grade cancers in the lobular group.

Table 4-4 Oncotype DX® RS, grade and tumour size of cohort

| | | Invasive Ductal Carcinoma n=395 (%) | Invasive Lobular Carcinoma n=100 |
|---------------------|-----------|-------------------------------------|----------------------------------|
| ODX RS | 1-10 | 76 (19.24) | 15 (15%) |
| | 11-25 | 254 (64.30) | 79 (79%) |
| | >25 | 65 (16.46) | 6 (6%) |
| | Mean (SD) | 18.88 (11.974) | 16.53 (7.276) |
| Tumour Grade | I | 48 (12.15) | 4 (4%) |
| | 2 | 289 (73.16) | 90 (90%) |
| | 3 | 58 (14.68) | 6 (6%) |
| Tumour Size | T1 | 178 (45.06%) | 16 (16%) |
| | T2 | 214 (54.18%) | 71 (71%) |
| | T3 | 3 (0.76%) | 13 (13%) |
| NPI | <3.4 | 114 (28.86%) | 10 (10%) |
| | 3.4-5.4 | 264 (66.84%) | 86 (86%) |
| | >5.4 | 17 (4.30%) | 4 (4%) |
| | Mean (SD) | 3.63 (.70074) | 3.81 (.55829) |
| Chemotherapy n (%) | | 87/395 (22.03) | 16/100 (16%) |

4.4.4 Oncotype DX® RS and NPI in Patients with IDC

Evaluation of the whole dataset suggested that the dependent variable (RS) was normally distributed, and the independent variables were not normally distributed. Pearson's correlation coefficient and Spearman's rho correlation coefficients were calculated for the dependent variable RS and the NPI, NLR and SII (Table 4.5). This suggested a weak correlation between the RS and NPI $r_s = [.348]$ $p < .001$, with no correlation seen with the inflammatory indices, NLR $r = .117$, $p = .010$ and the SII $r = .103$, $p = .020$. Spearman's rho correlation coefficient results confirmed this, with correlation coefficient of $r_s(493) = [.294]$, $p = [<.001]$, $r_s(495) = [.061]$, $p = [.017]$ and $r_s(495) = [.064]$, $p = [.148]$, for NPI, NLR, and SII respectively.

Table 4-5 Pearson’s Correlation Coefficient IDC cohort all ages

| Variable | Mean | Standard Deviation | Pearson’s Correlation Coefficient <i>r</i> (<i>p</i> value) | | | |
|----------|--------|--------------------|--------------------------------------------------------------|---------------------------|-------------------------------------|---------------------------|
| | | | ODX RS | NPI | NLR | SII |
| ODX RS | 18.89 | 11.974 | | .348 (<i>p</i> <.001) | <i>r</i> =.117 (<i>p</i> =.010) | .103 (<i>p</i> =.020) |
| NPI | 3.63 | .701 | .348 (<i>p</i> <.001) | | .045 (<i>p</i> =.187) | .021 (<i>p</i> =.340) |
| NLR | 2.91 | 1.696 | .117 (<i>p</i> =.010) | .045 (<i>p</i> =.187) | | .871 (<i>p</i> <.001) |
| SII | 807.74 | 535.08 | .103 (<i>p</i> =.020) | .021 (<i>p</i> =.340) | .871 (<i>p</i> <.001) | |

The results of the RS and NPI were explored for each age category. The cohort consisted of only node negative patients, which reduced the NPI to 0.2 x tumour size + Grade + 1, such that the only difference in NPI between the Grades is 0.2 x size.

In the over 50’s, most of the recurrence scores were in the low risk range, with 96% of Grade 1 and 85% of Grade 2 IDC having a score of under 25. Reviewing the data for the Grade 3 IDC’s, which comprised a quarter of this cohort, confirms that almost half of the Oncotype DX® RS were low risk in the over 50 age group (Figure 4.3).

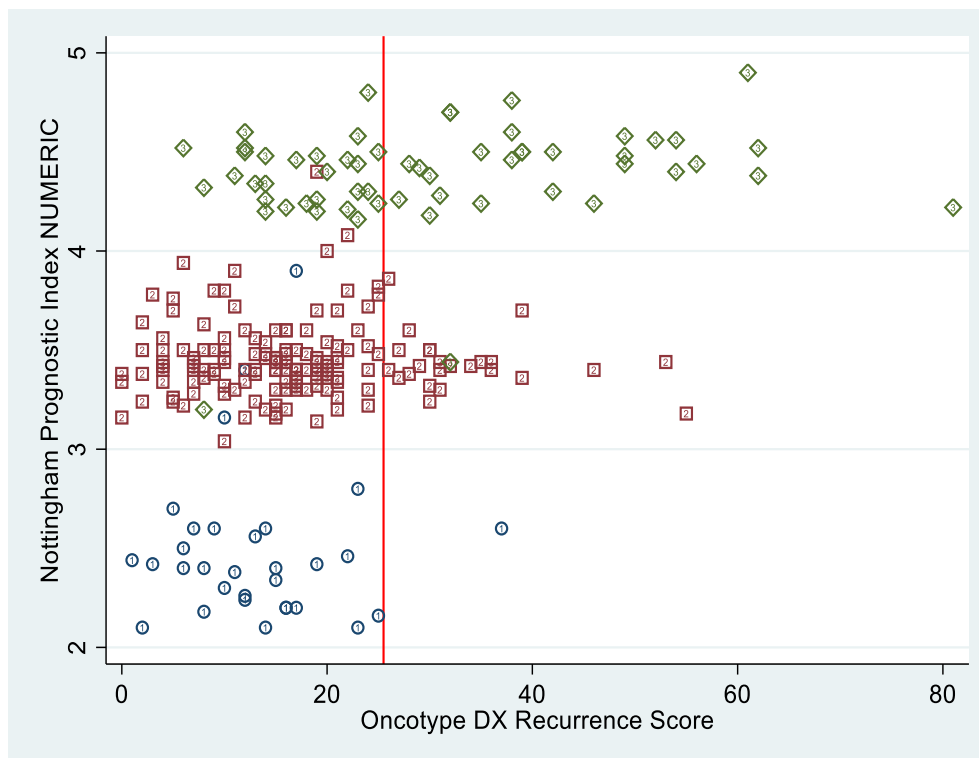


Figure 4.3 Relationship between Oncotype DX® RS and NPI in ductal cancers for patients aged 50 years and over
Note: Grade 1 (Blue), Grade 2 (Red), Grade 3 (Green) (red line denotes 25 RS cutoff for chemotherapy)

Interestingly, in the under 50 age group, 66% of Grade 1 and 2 were low risk, however all the Grade 3 IDC were ODX high risk (Table 4.3; Figure 4.4).

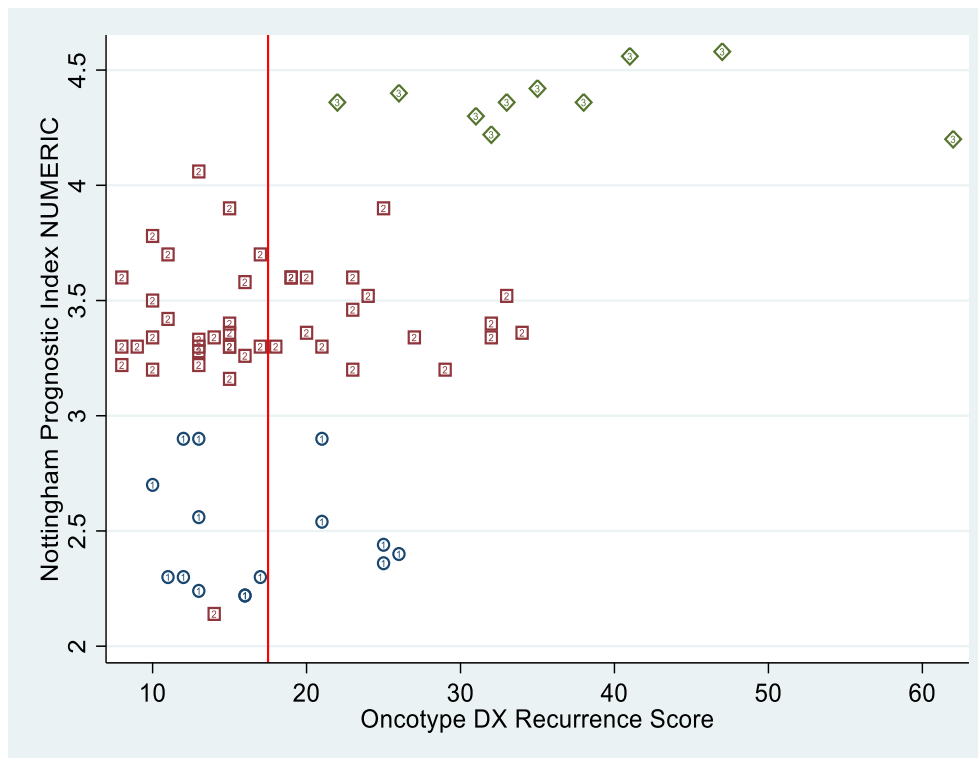


Figure 4.4 Relationship between Oncotype DX® RS and NPI in ductal cancers for patients under 50 years of Age
Note: Grade 1 IDC Blue; Grade 2 IDC Red; Grade 3 IDC Green (red line denotes 18 RS cutoff for chemotherapy)

4.4.5 Oncotype DX® Recurrence Score and NPI in Patients with ILC

The relationship between Grade and Oncotype DX® RS in the ILC group is less evident (Figure 4.5; Figure 4.6). Most of the patients in the ILC group had low to intermediate RS with moderate NPI scores in both age categories. These NPI scores in the lobular group are mainly dependent on tumour size, as 94% of the ILC cohort were Grade 1 or 2. There were four Grade 1 cancers in the total lobular cohort, with all these patients in the over 50 age group. There were 6 patients with Grade 3 ILC, with 5 in the over 50's.

The single patient in the under 50 cohort with pleomorphic Grade 3 ILC presented with pulmonary and bone metastases 3 years post diagnosis. She was a 41 year old lady with no family history, who underwent conservative breast surgery for a node negative 12mm Grade 3 pleomorphic ILC, ER6, PR7. The Oncotype DX® RS was 21. The NPI was 4.24 [(1.2 x 0.2) + 3 + 1 (node negative)]. The SII, NLR, MLR, PLR

were all within normal limits. She received adjuvant chemotherapy followed by endocrine therapy. She was on extended endocrine therapy when she developed widespread metastatic disease and subsequently died 6 years post diagnosis. The prognostic tools in this case failed to identify this patient as high risk for recurrence and death. Although the pleomorphic subtype has a higher risk of recurrence, this patient was node negative with an intermediate RS and moderate risk NPI. She received dose dense chemotherapy.

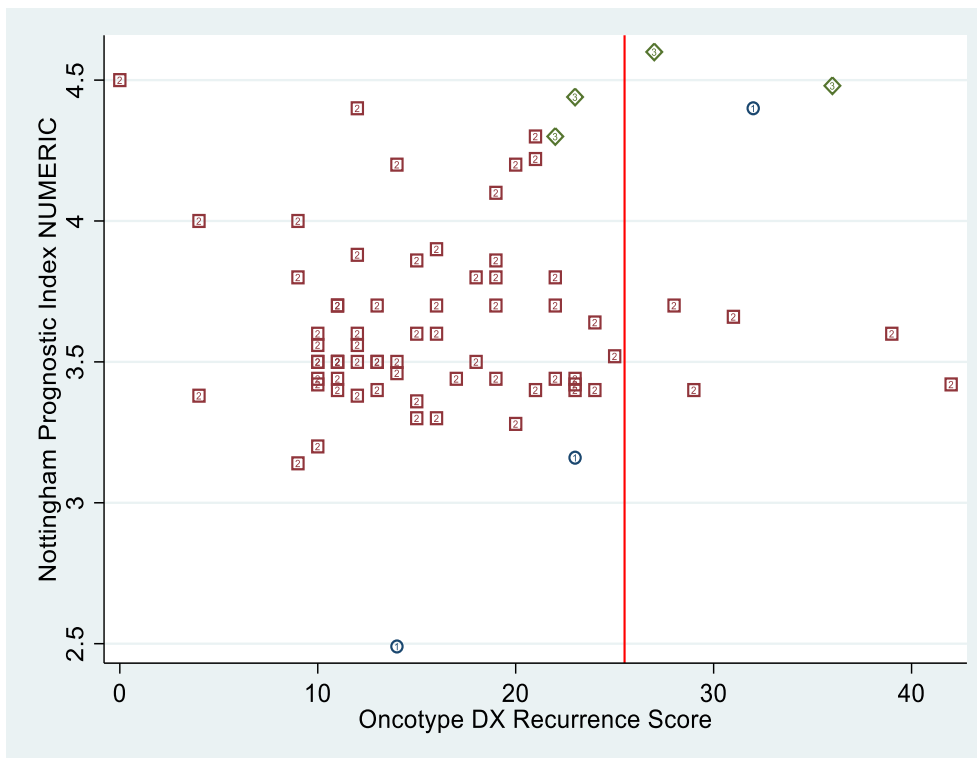


Figure 4.5 Comparison of Oncotype DX® RS and NPI in ILC patients 50 years and over

Note: Grade 1 Blue; Grade 2 Red; Grade 3 Green

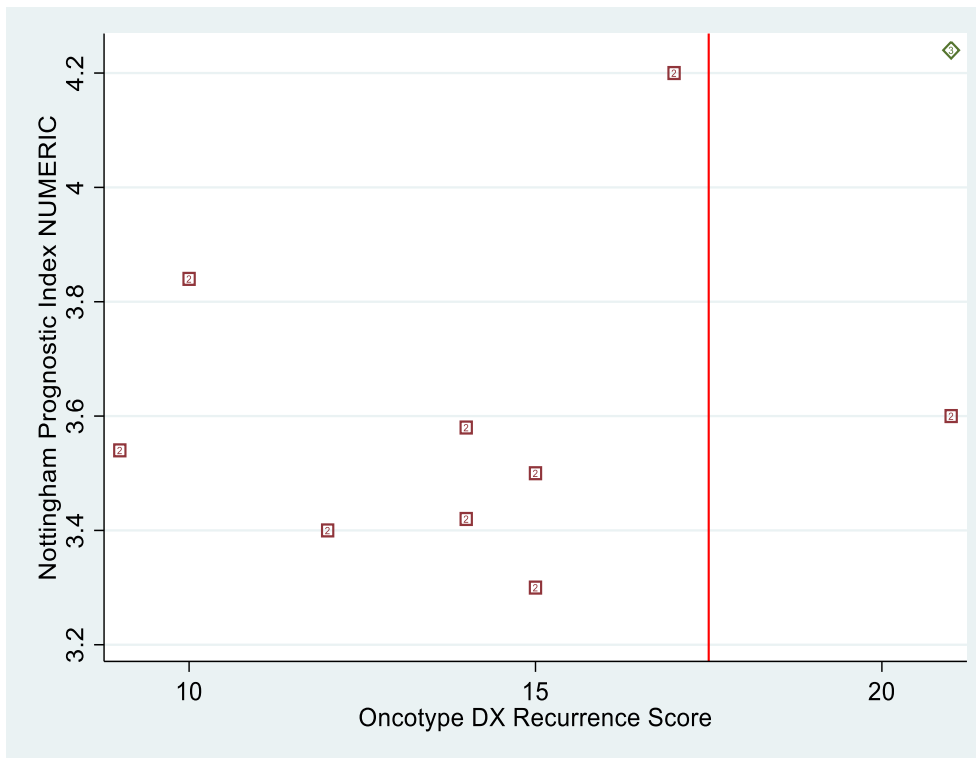


Figure 4.6 Comparison Oncotype DX® RS and NPI in ILC Patients under 50 years of age.

Note: Grade 1 Blue; Grade 2 Red; Grade 3 Green

4.4.6 Correlation of Oncotype Recurrence Score by Age and Tumour Group

Oncotype DX® RS is used as a predictor of response to chemotherapy. Adjuvant chemotherapy for patients in the under 50 age groups is recommended with $RS \geq 16$, and $RS > 25$ in patients that are 50 years and above. Oncotype testing resulted in only 24% (97/495) of the total cohort being considered for chemotherapy. Analysing the data for the two histological groups, confirms that 72% of the IDC group and 88% of the ILC cohort avoided chemotherapy. As expected, more ductal than lobular patients received chemotherapy.

4.4.6.1 Oncotype DX® RS and NLR and SII

The inflammatory indices and Oncotype DX® RS data was evaluated separately for the ILC and IDC in the two age groups, under 50 and ≥ 50 years of age. No correlation was seen between the RS and the NLR (Figure 4.7. Figure 4.8), or the RS and the SII in the IDC or ILC cohort, for either age group. Spearman's correlation coefficients for RS and NLR in the IDC and ILC under 50 age cohort were $rs(76)=[.06]$, $p=[.63]$ and

$rs(9)=[-.24]$, $p=[.51]$, respectively (Figure 4.7). In the over 50 cohort, Spearman's correlation coefficient for IDC and ILC, were $rs(315)=[.14]$, $p=[.03]$, and $rs(87)=[.09]$, $p=[.43]$ (Figure 4.8).

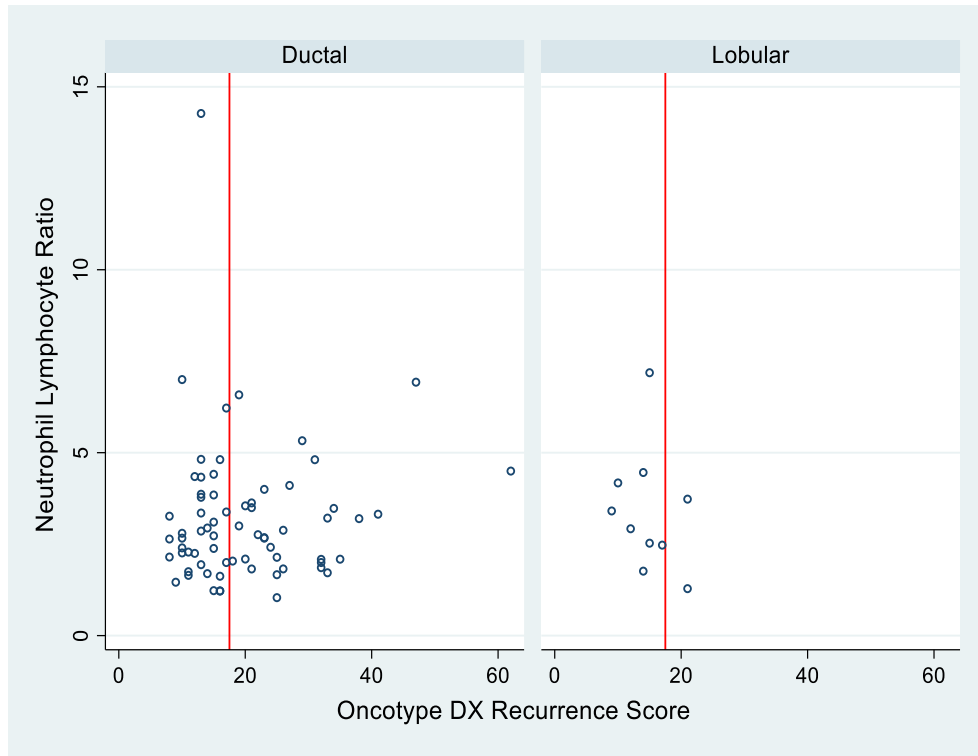


Figure 4.7 NLR and Oncotype DX® RS correlation for IDC and ILC under 50 years

Note: Spearman's correlation coefficient under 50 years: IDC $rs(76) = [.06]$, $p=[.063]$; ILC $rs(9)=[-.24]$, $p=[.51]$ (red line denotes RS 18 cutoff for chemotherapy).

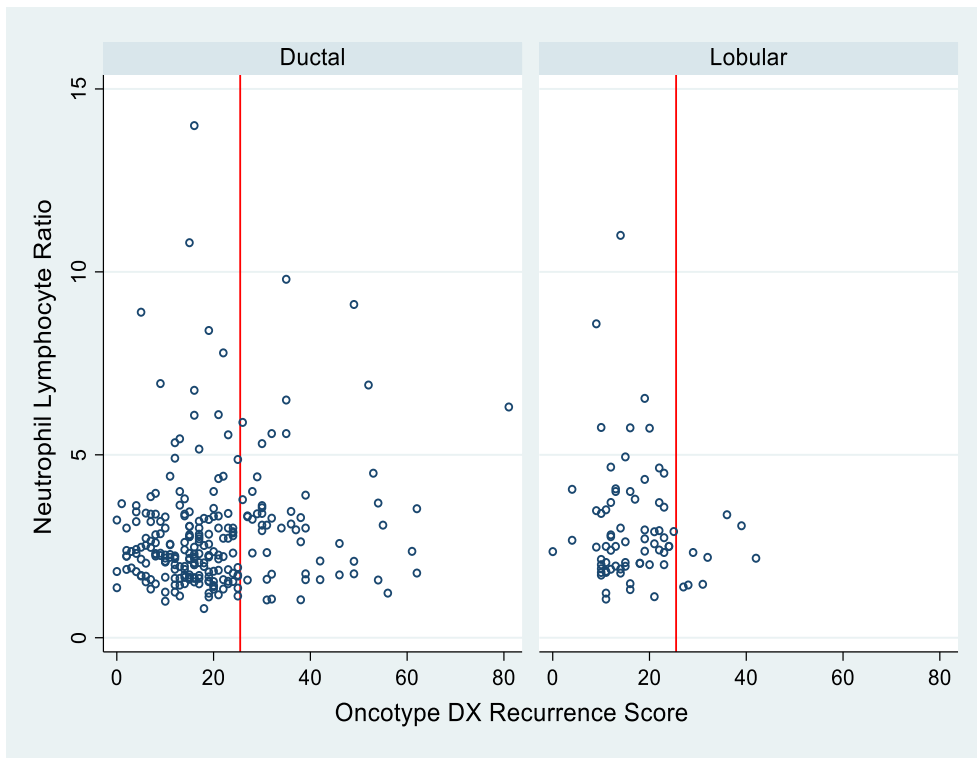


Figure 4.8 NLR Oncotype DX® RS correlation for IDC and ILC in the over 50 age group.

Note: Spearman’s correlation coefficient IDC $r_s(315)=[.14]$, $p=[.03]$; ILC $r_s(87)=[-0.09]$, $p=[.43]$

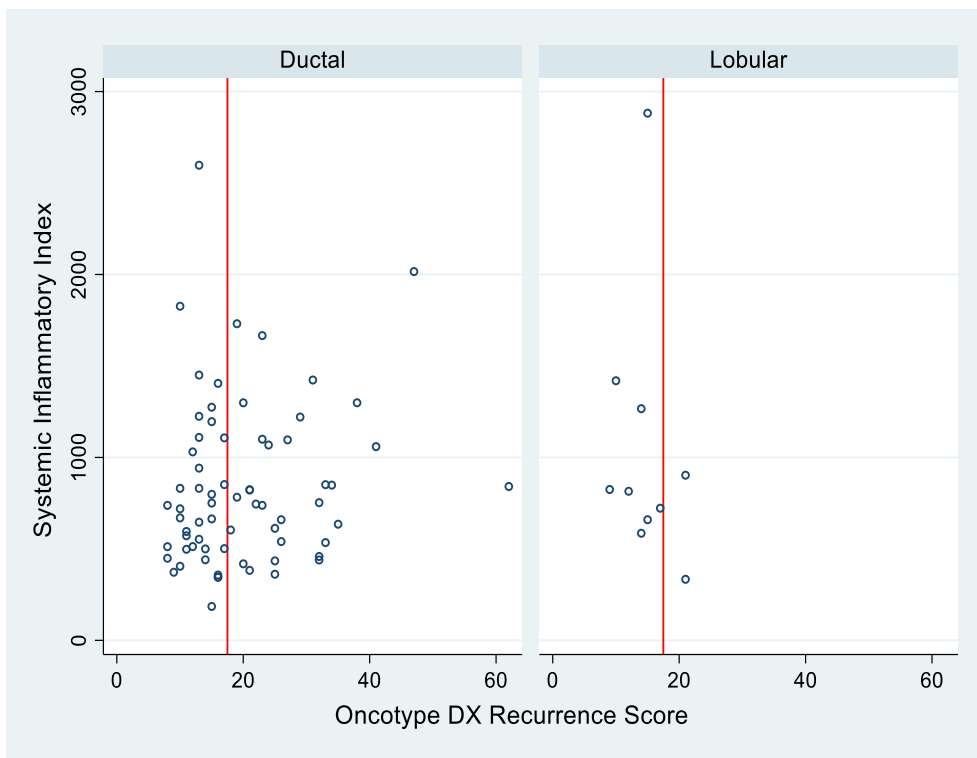


Figure 4.9 SII Oncotype DX® RS correlation for IDC and ILC under 50 years

Note: Spearman’s correlation coefficient IDC $r_s(76)=[0.15]$, $p=[.230]$; ILC $r_s(9)=[-.21]$, $p=[.570]$

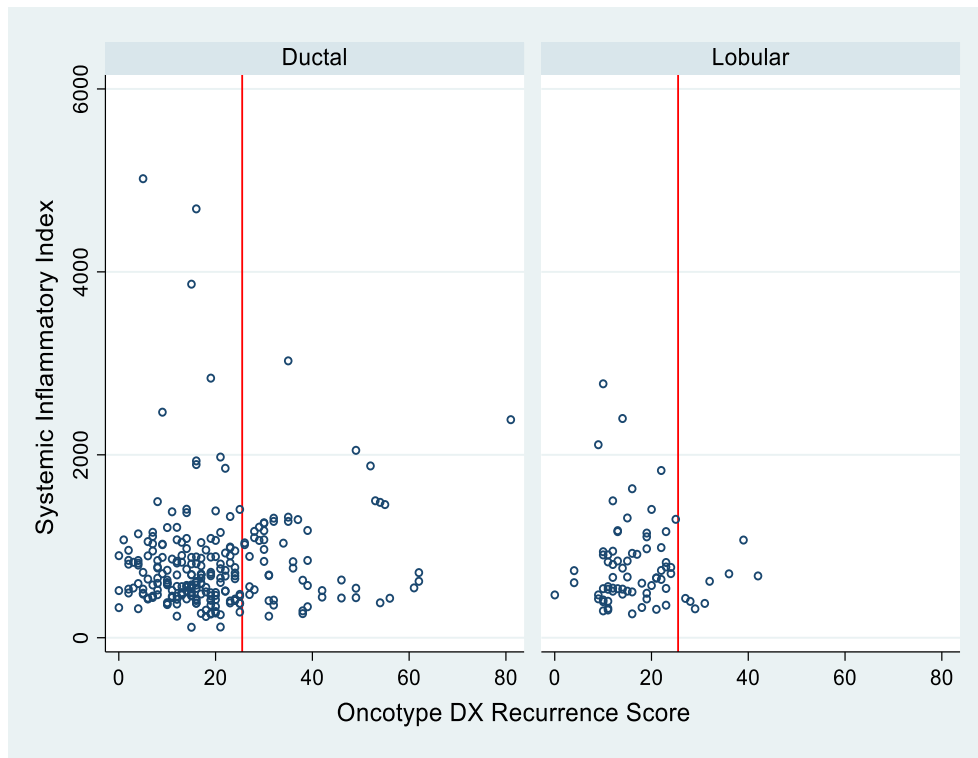


Figure 4.10 SII Oncotype DX® RS correlation IDC and ILC over 50 age group.

Note: Spearman’s correlation coefficient IDC $rs(315)=[.091]$, $p=[.150]$; ILC $rs(87)=[-.05]$, $p=[.660]$

4.4.6.2 *Oncotype DX® RS and Nottingham Prognostic Index*

Analysing the data for correlation between the NPI and RS for the two histology groups was assessed. Spearman’s rho correlation coefficient was calculated for IDC and ILC in the under 50 age group, $rs(76)=[.48]$, $[p<01]$, and $rs(9)=[.43]$, $p=[.221]$, respectively. The calculation was repeated for the over 50 age group, $rs(315)=[.43]$, $[p<01]$, and $rs(87)=[.16]$, $p=[.18]$. (Figure 4.11. Figure 4.12). The results suggest that there is some linear association with NPI in both age groups in the ductal group.

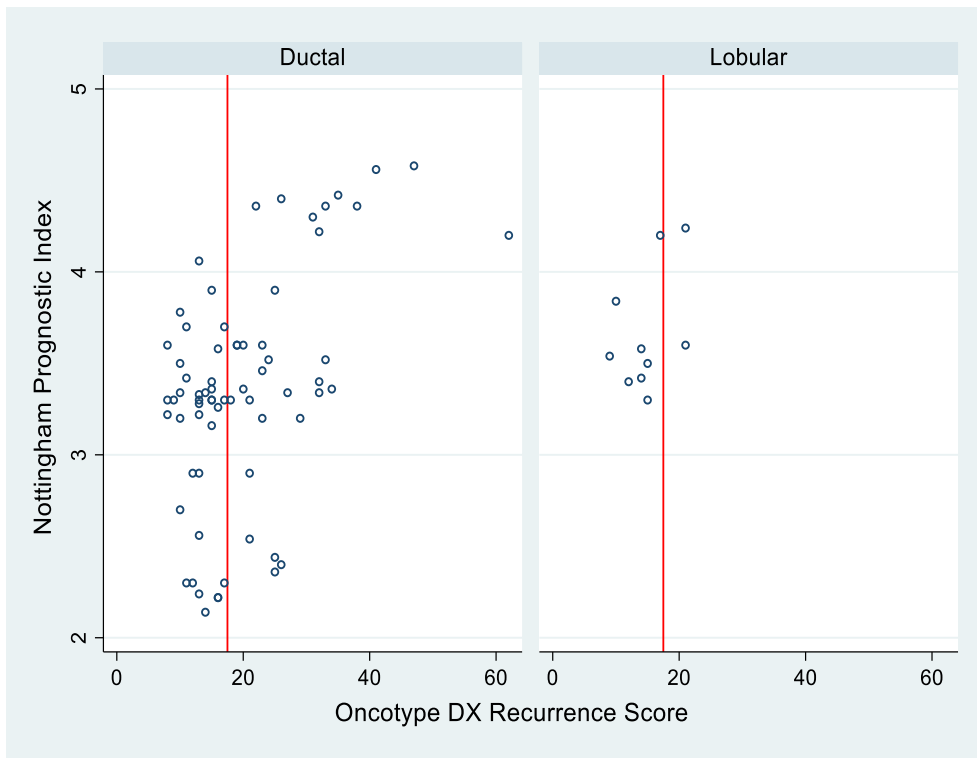


Figure 4.11 NPI Oncotype DX® RS Correlation IDC and ILC under 50 age group

Note: Spearman's correlation coefficient IDC $r_s(76)=[.48]$, [$p<.01$]; ILC $r_s(9)=[.43]$, [$p=.221$]

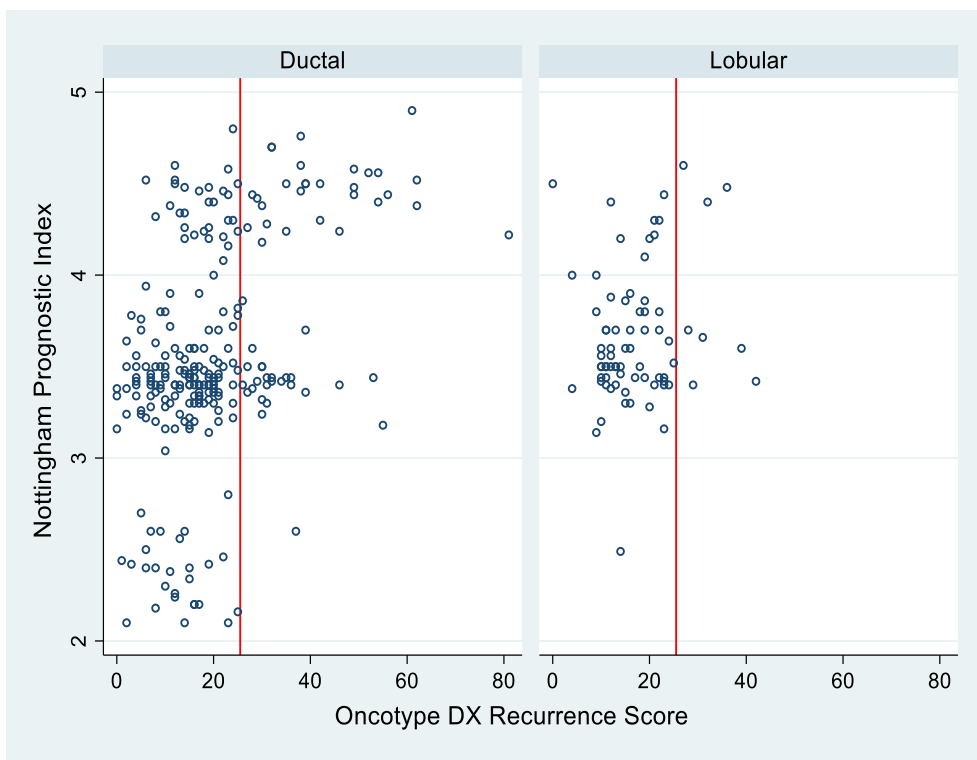


Figure 4.12 NPI Oncotype DX® RS Correlation Coefficient in the over 50 age group.

Note: Spearman's rho correlation coefficient IDC $r_s(315)=[.43]$, [$p<.01$]; ILC $r_s(87)=[.16]$, [$p=.18$]

4.4.6.3 Oncotype DX® RS and Tumour Grade

The Oncotype DX® recurrence scores were plotted for each age category in both the IDC and ILC cohort to visualise the effect of grade. Both graphs illustrate how most of the lobular cancers were Grade 1 or 2 in all ages, with no Grade 1 tumours seen in the under 50. Figures 4.13 and 4.14 demonstrate how the Oncotype DX® RS in ILC appears to be unrelated to tumour grade, with most of the ILC cohort having a moderate RS. However, this may be a consequence of the selection process for testing this tumour group.

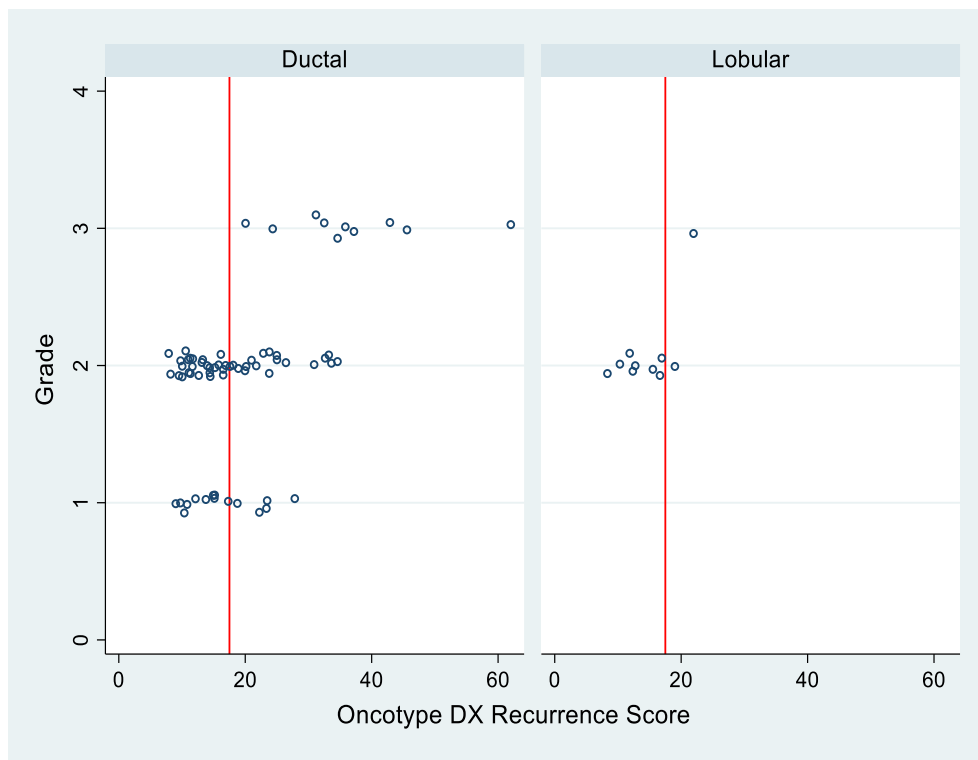


Figure 4.13 Grade of tumour for IDC and ILC with Oncotype DX® RS under 50 years of Age



Figure 4.14 Grade of tumour for IDC and ILC by Oncotype DX® RS ≥50yrs of Age

4.4.6.4 *Oncotype DX® RS Correlation Tumour Size*

The data was analysed to assess whether there was any correlation between tumour size and the Oncotype DX® RS for both age categories and tumour subtypes. Visual inspection of the results suggest very little evidence of any linear association between tumour size and RS for both lobular and ductal tumours, in all age groups. Spearman’s rho correlation coefficients for RS and pathology size in the IDC and ILC groups for under 50 years were $rs(76)=[.01]$, $p=[.91]$, and $rs(9)=[-.14]$, $p=[.70]$, respectively. Repeating the analysis for the over 50 age group confirmed that for IDC and ILC, Spearman’s rho correlation coefficients were $rs(315)=[.07]$, $p=[.27]$, and $rs(87)=[-.14]$, $p=[.70]$ (Figure 4.15; Figure 4.16).

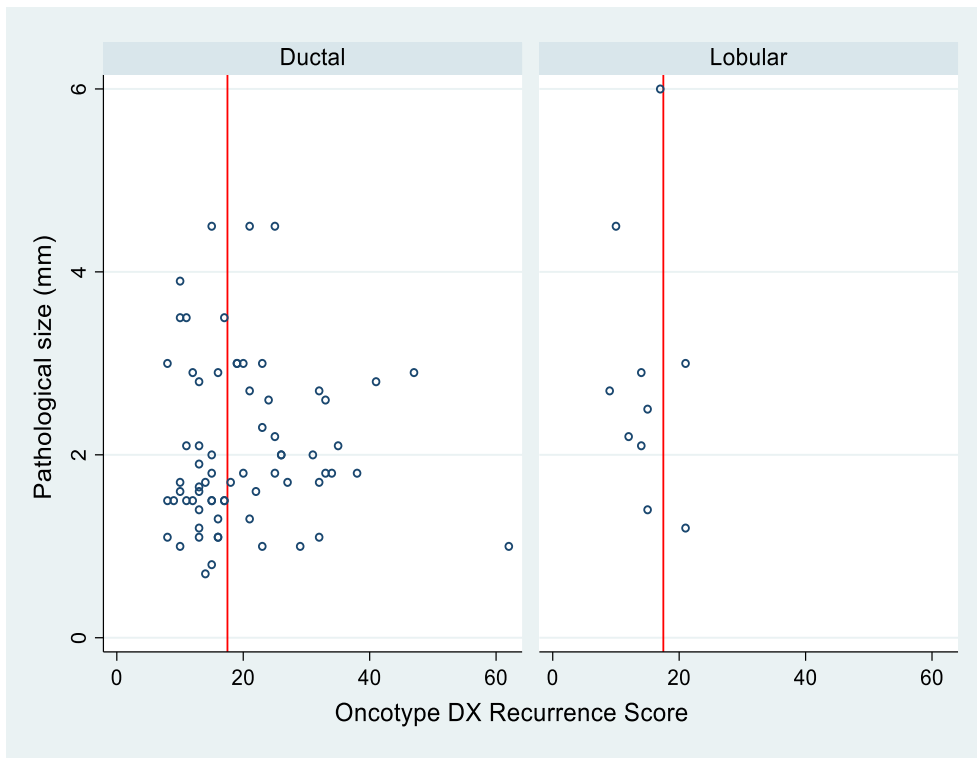


Figure 4.15 Oncotype DX® RS and size by histology group under 50 years of age

Note: Spearman's rho correlation coefficient IDC $rs(76)=[.01]$, $[p=.91]$; ILC $rs(9)=[-.14]$, $[p=.70]$

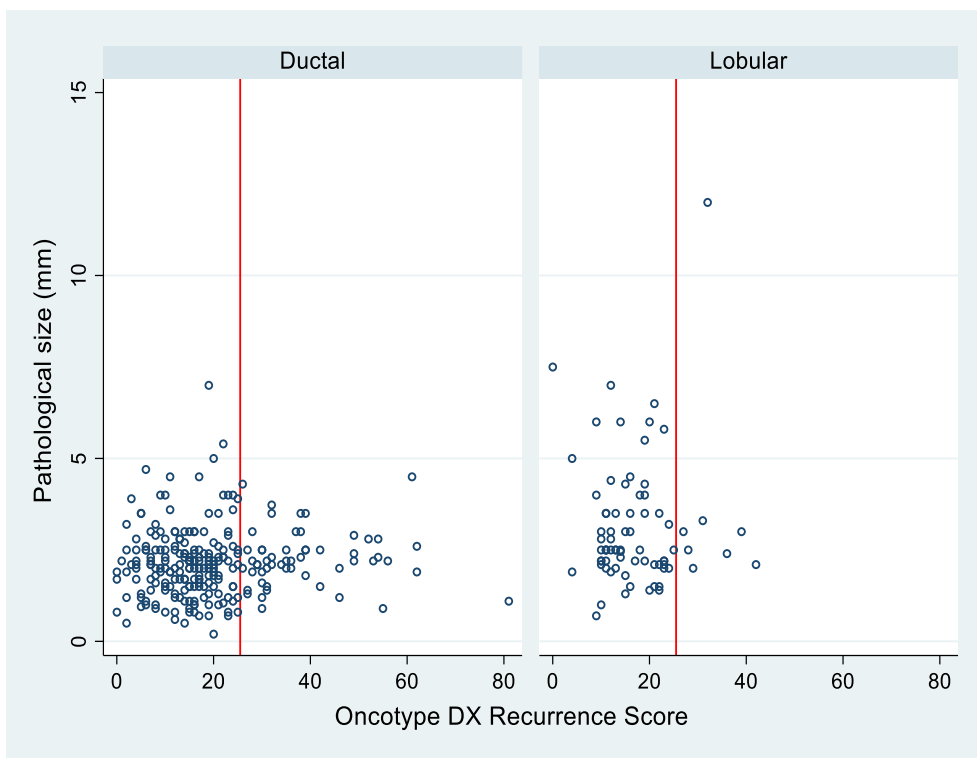


Figure 4.16 Oncotype DX® RS and size correlation by histology group in the over 50 age group

Note: Spearman's rho correlation coefficient IDC $rs(315)=[.07]$, $[p=.27]$; ILC $rs(87)=[.01]$, $[p=.93]$

4.4.6.5 Oncotype DX® RS Correlation with Platelet to Lymphocyte Ratio

The data was evaluated to assess any potential correlation between the Oncotype DX® RS and the PLR in both age categories and tumour subtypes. Spearman's rho correlation coefficients confirmed negligible correlation for each age group and for both subtypes. In the under 50 age group; for IDC $rs(76)=[.19]$, $p=[.12]$, and for ILC $rs(9)=[-.22]$, $p=[.53]$, (Figure 4.17) and for the over 50 groups $rs(315)=[.02]$, $p=[.78]$, and $rs(87)=[.10]$, $p=[.38]$, (Figure 4.17).

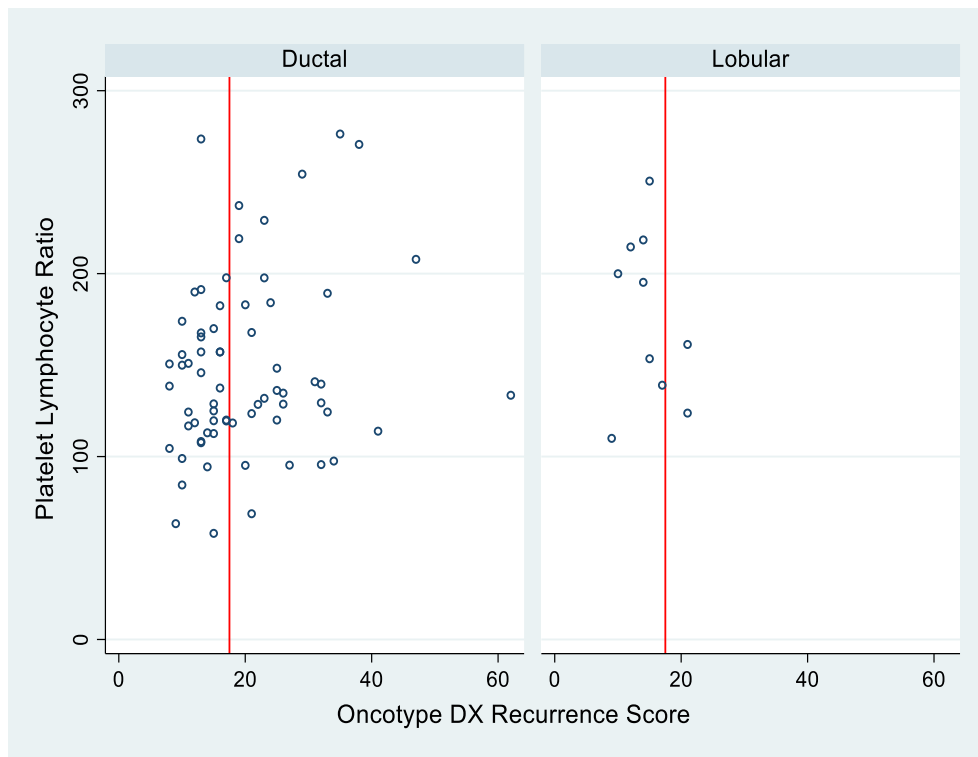


Figure 4.17 RS and PLR correlation by histology group in the under 50 year age group

Note: Spearman's rho correlation coefficient IDC $rs(76)=[.19]$, $[p=.12]$; ILC $rs(9)=[-.22]$, $[p=.53]$

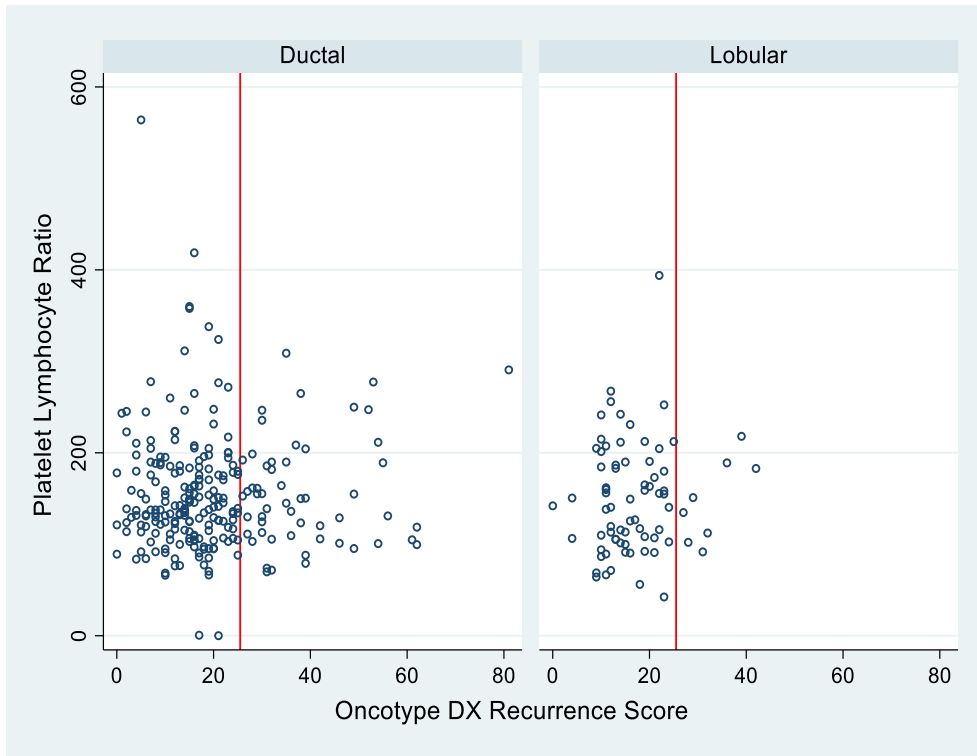


Figure 4.18 RS and PLR correlation by histology in the over 50 age group

Note: Spearman’s rho correlation coefficient IDC $rs(315)=[.02]$, $[p=.78]$; ILC $rs(87)=[.10]$, $[p=.38]$

4.4.6.6 *Oncotype DX® RS Correlation MLR by histology group*

There was no correlation seen with Oncotype DX® RS and MLR in both age categories for IDC and ILC tumours (Figure 4.19. Figure 4.20). Spearman’s rho correlation coefficients confirmed no correlation for each age group and for both subtypes. In the under 50 age group; for IDC $rs(76)=[-.03]$, $p=[.81]$, and for ILC $rs(9)=[-.14]$, $p=[.70]$ (Figure 4.19), and for the over 50 groups $rs(315)=[.01]$, $p=[.88]$, and $rs(87)=[-.07]$, $p=[.53]$ (Figure 4.20).

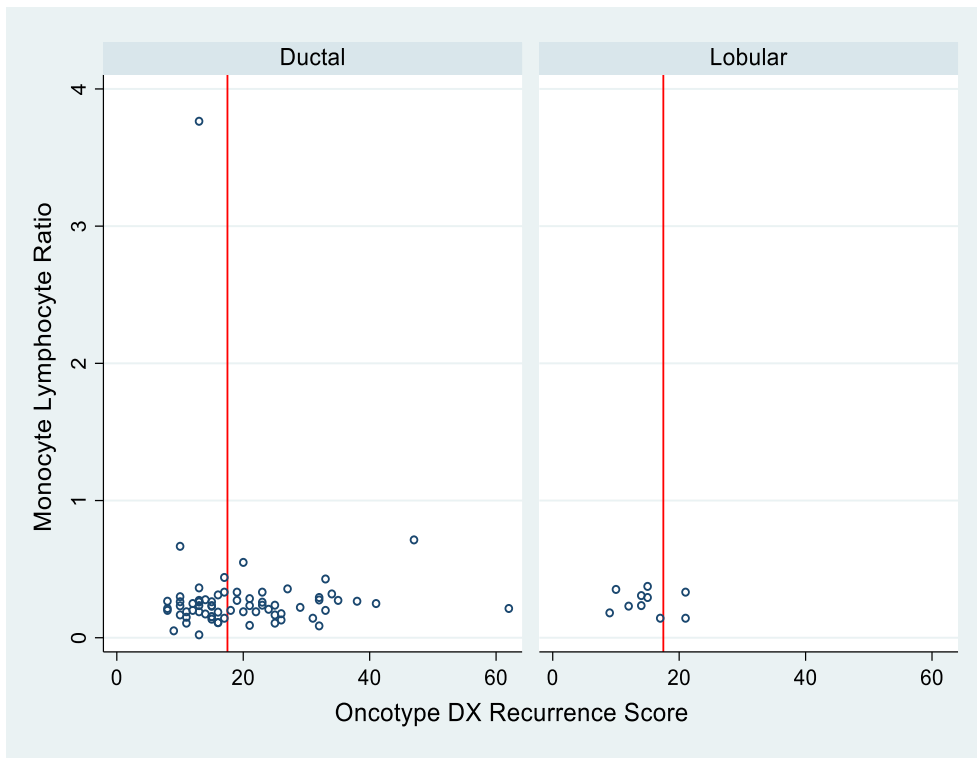


Figure 4.19 RS and MLR correlation by histology group in the under 50 age group

Note: Spearman's rho correlation coefficient IDC $rs(76)=[-.03]$, $[p=.81]$; ILC $rs(9)=[-.14]$, $[p=.70]$

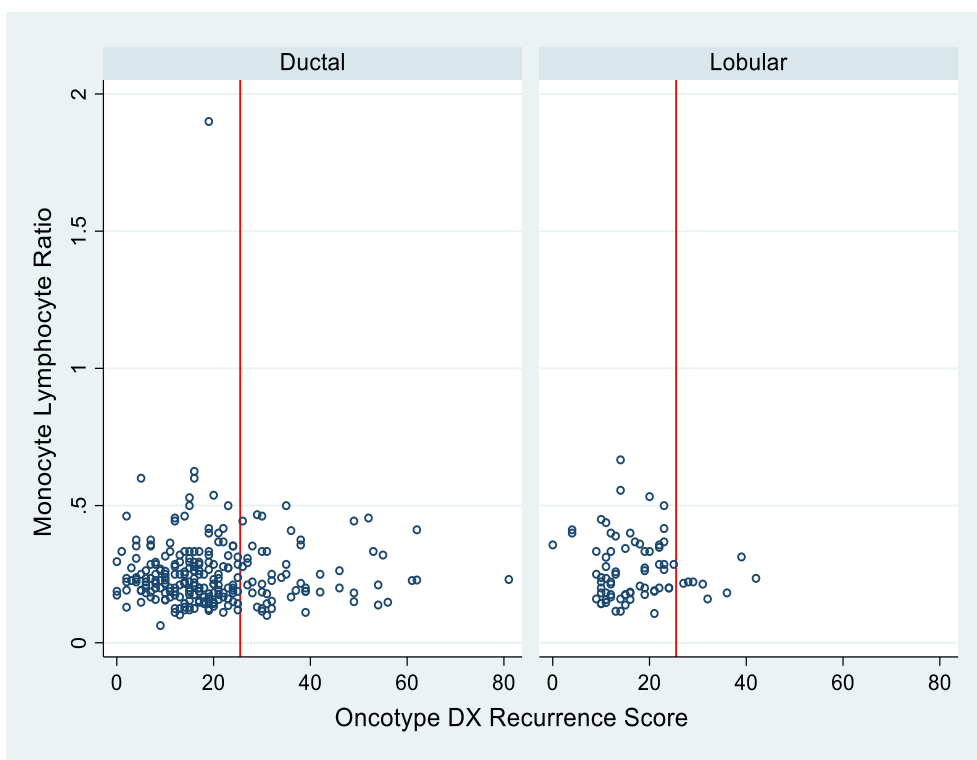


Figure 4.20 RS and MLR by Histology Group in the over 50 age group

Note: Spearman's rho correlation coefficient IDC $rs(315)=[.01]$, $[p=.88]$; ILC $rs(87)=[-.07]$, $[p=.53]$

4.4.6.7 Oncotype DX® RS and RDW Correlation

There was no correlation seen between the Oncotype DX® RS and RDW for IDC and ILC, in both age categories (Figure 4.21. Figure 4.22). Spearman's rho correlation coefficients confirmed no correlation for each age group and for both subtypes. In the under 50 age group; for IDC $rs(76)=[.20]$, $p=[.10]$, and for ILC $rs(9)=[.14]$, $p=[.69]$, (Figure 4.21) and for the over 50 groups $rs(315)=[.02]$, $p=[.78]$, and $rs(87)=[.10]$, $p=[.38]$, (Figure 4.17).

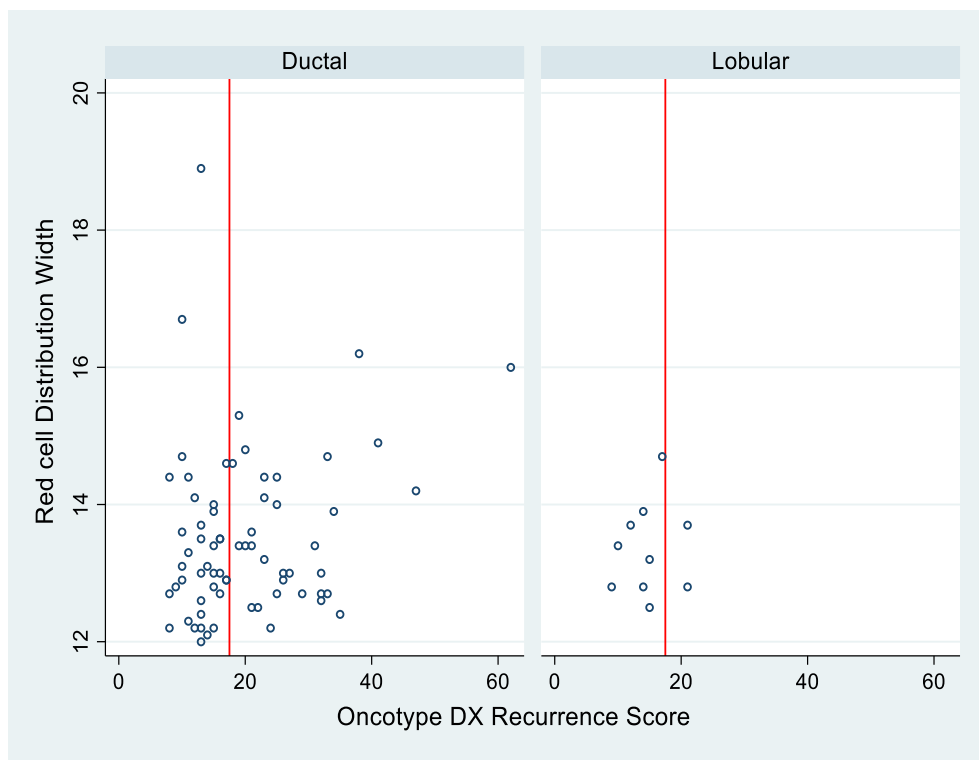


Figure 4.21 RS and RDW correlation by Histology Group under 50 age group

Note: Spearman's rho correlation coefficient IDC $rs(76)=[.20]$, $[p=.10]$; ILC $rs(9)=[.14]$, $[p=.69]$

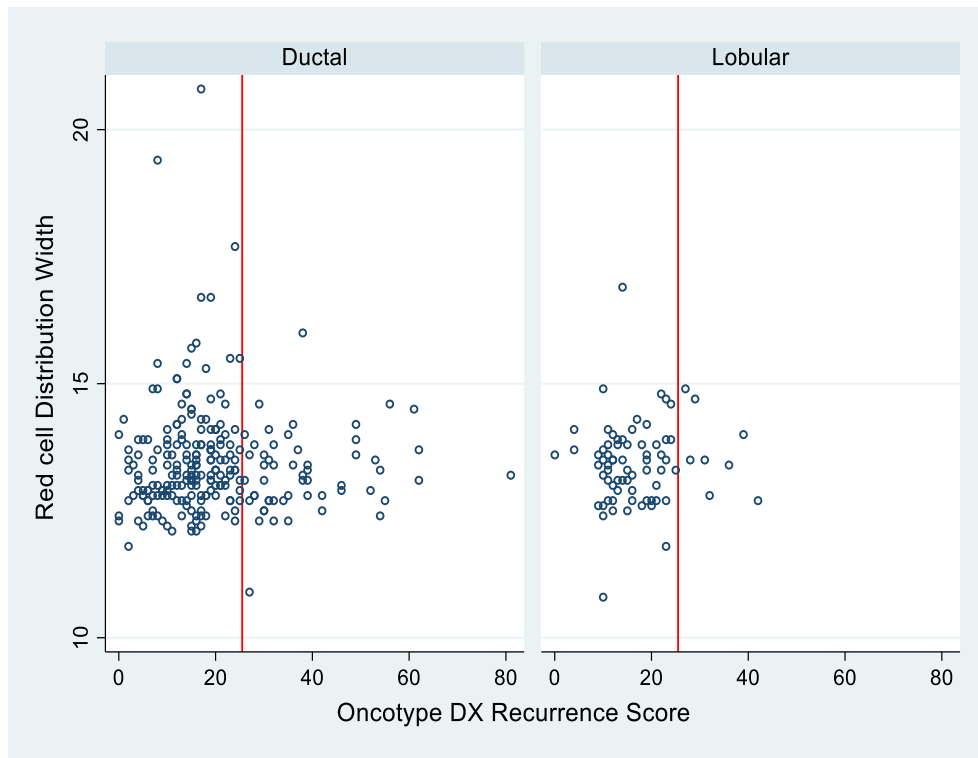


Figure 4.22 RS and RDW correlation by Histology Group in the over 50 age group
Note: Spearman’s correlation coefficient IDC $r(315)=[.01]$, $[p=.94]$; ILC $r(87)=[.07]$, $[p.57]$

4.4.7 Sub-Analysis of the Lobular Cohort

4.4.7.1 Tumour Characteristics

Of the 100 lobular cancers in the study, most were Grade 2 (90%). In the under 50 age group (n=11), 81.82% (n=9) were Grade 2, and 18.18% (n=2) were Grade 3 (one pleomorphic variant), with no Grade 1 tumours (Figure 4.23).

In the over 50 years of age cohort (n=89), 4.49% (n=4) were Grade 1, 91.01% (n=81) were Grade 2 and 4.49% (n=4) were Grade 3 (of these, two were pleomorphic).

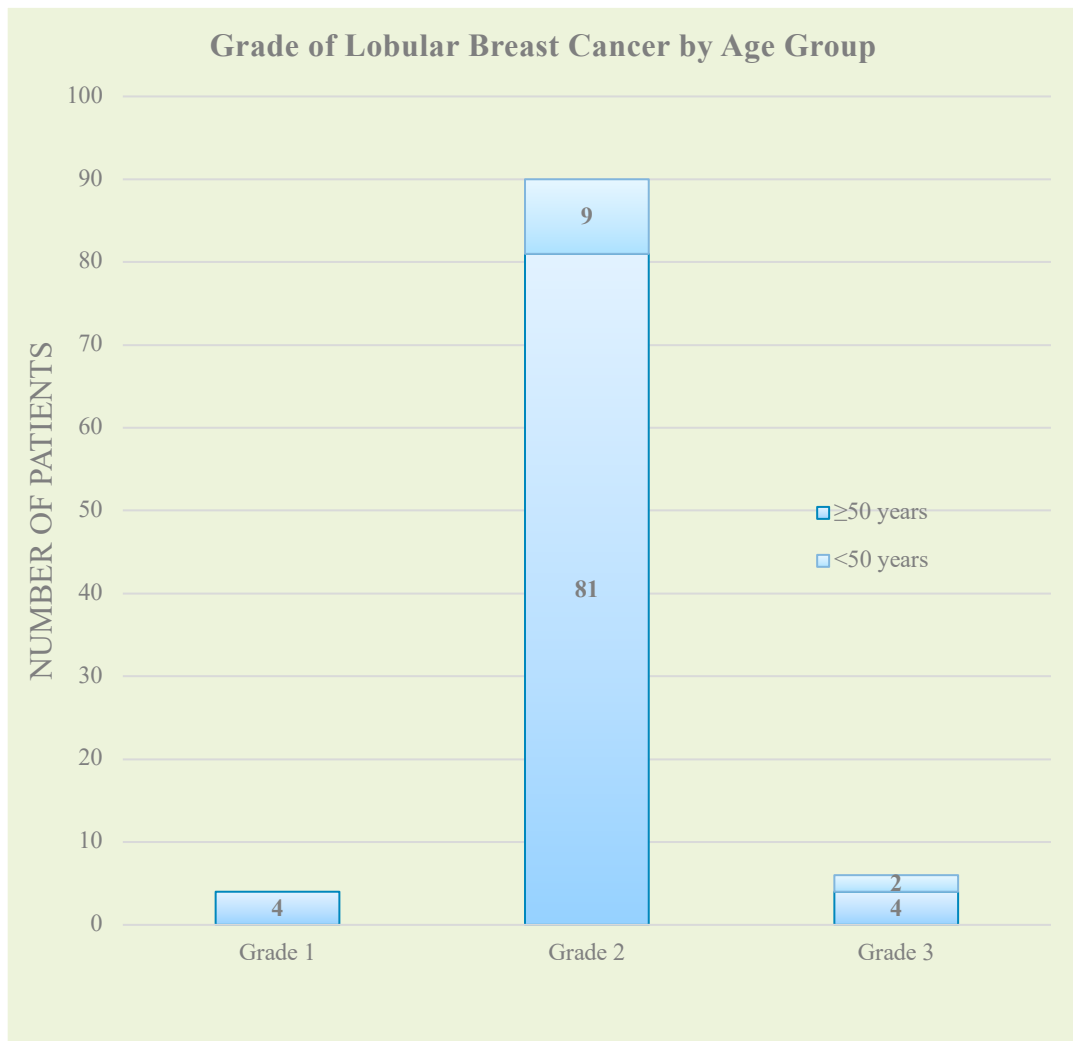


Figure 4.23 Lobular cancer tumour grade of cohort by age category

The low percentage of Grade 3 tumours in the study population is not unexpected. Most lobular cancers are Grade 1 or 2. In addition, it is feasible that discussions in the MDT may have resulted in cases considered high risk being offered upfront chemotherapy without genomic testing. It is interesting that the two pleomorphic lobular cancers in the cohort were tested for Oncotype DX® RS with both having RS greater than 25 and receiving chemotherapy. The first patient, a 68 year old lady with a past history of hypothyroidism. She was a symptomatic breast patient diagnosed with a 30mm node negative Pleomorphic Grade 3 ILC treated with a mastectomy and sentinel node biopsy in 2018. NPI 4.6. Oncotype DX® RS 27. Systemic inflammatory indices normal. She received adjuvant chemotherapy. She is alive and well 5 years later. The other patient, a 72 year old lady with comorbidities (hypertension and significant osteoarthritis), presented with a left breast lump. Pathology confirmed a node negative 21mm pleomorphic Grade 3 ILC. Final tumour size 21mm. ER 5/8,

Progesterone receptor negative (0/0). The systemic inflammatory indices were normal, NPI 4.42, in the moderate risk category. ODX RS 42. The patient received adjuvant chemotherapy and is alive and well 7 years later. Practically, Oncotype DX® RS testing is occasionally utilised to assist the oncologist when discussing adjuvant therapy for patients with multiple comorbidities and risk factors for chemotherapy.

4.4.7.2 Treatment

Surgical management of the lobular cohort confirmed that 64% of the whole cohort were treated with mastectomy, compared with 20.25% of the IDC group of patients (Table 4.1; Table 4.2). Mean tumour size was higher in the ILC patients, which partly explains the difference. The mastectomy rate in the under 50 age group was 81.82%, with 9 of the 11 patients undergoing mastectomy. Similar mastectomy rates were also noted in the imaging study (Chapter 3).

4.4.7.3 Survival Analysis of the Lobular Cohort

Early studies suggest that 5 year survival rates for lobular cancer are more favourable when compared with IDC (Pestalozzi et al., 2008). However, long term outcomes appear to be worse for this subtype, with an increase in recurrences years after diagnosis (Chen et al., 2017; Pramod et al., 2021). The cancer related deaths in the ILC cohort occurred between 2 and 6 years from diagnosis (Table 4.6). The commonest site of metastatic spread was bone, followed by lung and liver. The data was collected up to 2020, as such the mortality rate may be slightly skewed.

There were 4 deaths in the lobular cohort of patients (4%). Tumour characteristics of this group of patients (n=4) were very similar, with all the lobular cancers being ER and PR positive. The NPI results were in the moderate risk category. The systemic inflammatory indices were normal in 3 of the 4 patients (Table 4.6). The patient with the raised NLR, MLR, and SII, had a low ODX RS of 5. This lady developed bone and brain metastases within eighteen months and died two years following the diagnosis. There was no family history, medication history, or significant comorbidities in this group of patients.

Table 4-6 Cohort characteristics of deceased patients with lobular cancer

| Cohort No. | Age at Diagnosis | Operative Details | Tumour Grade | ER/PR | NPI | ODX RS | SII | CXT | Site of recurrence | OS Years |
|------------|------------------|-------------------|--------------|-------|------|--------|----------------------|-----|--------------------|----------|
| 2 | 67 | Mast | 2 | 8/8 | 3.6 | 12 | N | No | Lung | 6 |
| 42 | 70 | Mast | 2 | 8/8 | 3.6 | 39 | N | Yes | Bone/Lung | 4 |
| 91 | 41 | WLE | 3 | 6/7 | 4.24 | 21 | N | Yes | Bone/Liver/Lung | 6 |
| 394 | 67 | Mast | 2 | 8/5 | 5 | 5 | NLR/MLR & SII raised | No | Bone/Brain | 2 |

Note: Cohort characteristics of deceased ILC patients. Operative details: Mast= mastectomy; WLE=conservative breast surgery. All the patients in this category were taking endocrine therapy at the time of recurrence.

4.4.7.4 Systemic Inflammatory Indices in the Lobular Cohort

Kendall's Tau and Spearman's Rank correlation coefficient analysis on the whole data (IDC and ILC), and for the lobular cohort of patients suggested no correlation between RS and SII and RS and NLR, in both IDC and ILC, and for the two age categories. The statistical results of these analyses are provided in Appendix 5. The findings suggested that there was no correlation with RS and the NLR or SII in both subtypes, and age groups.

Statistical analysis of the NLR and SII was performed with a 1/sqrt transformation, as the two variables are not normally distributed (Shapiro-Wilk $p < 0.01$). (1/sqrt transformation). Analysis confirmed that Oncotype DX® RS is not normally distributed ($p < 0.01$), with no suitable transformation identified. Graphical representation of the data confirms that there is no correlation between the RS and the SII and the RS and the NLR in the lobular cohort studied (Figure 4.25; Figure 4.26).

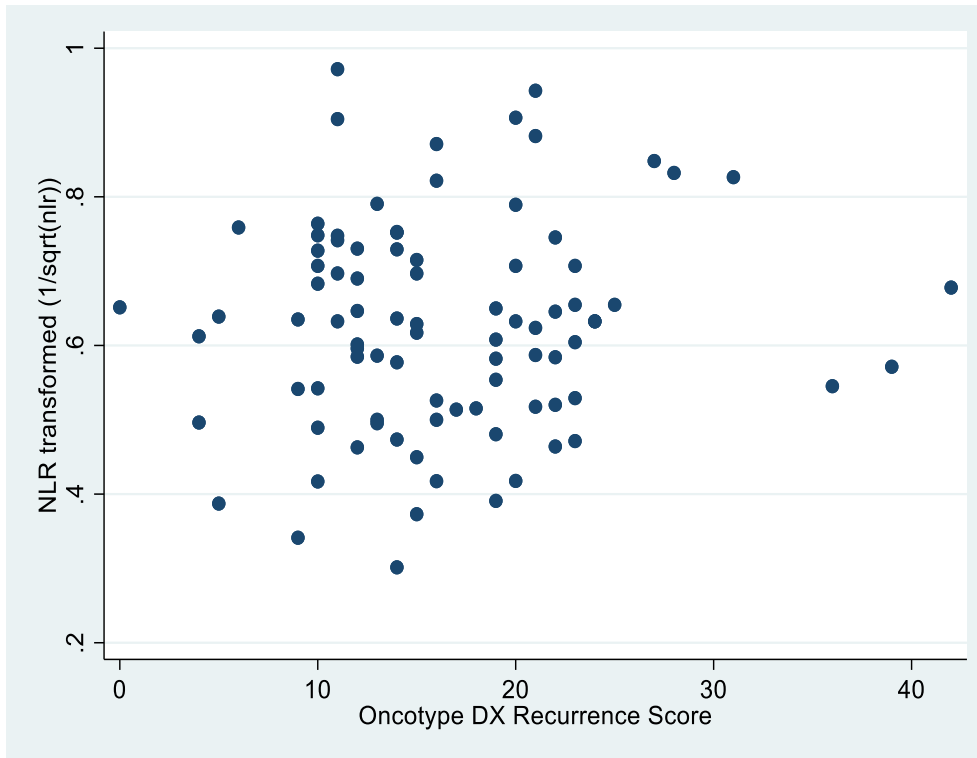


Figure 4.24 Correlation between Oncotype DX® RS and NLR Lobular Cohort

Note: Spearman's rho correlation coefficient $rs(98)=[.081]$, $p<0.001$

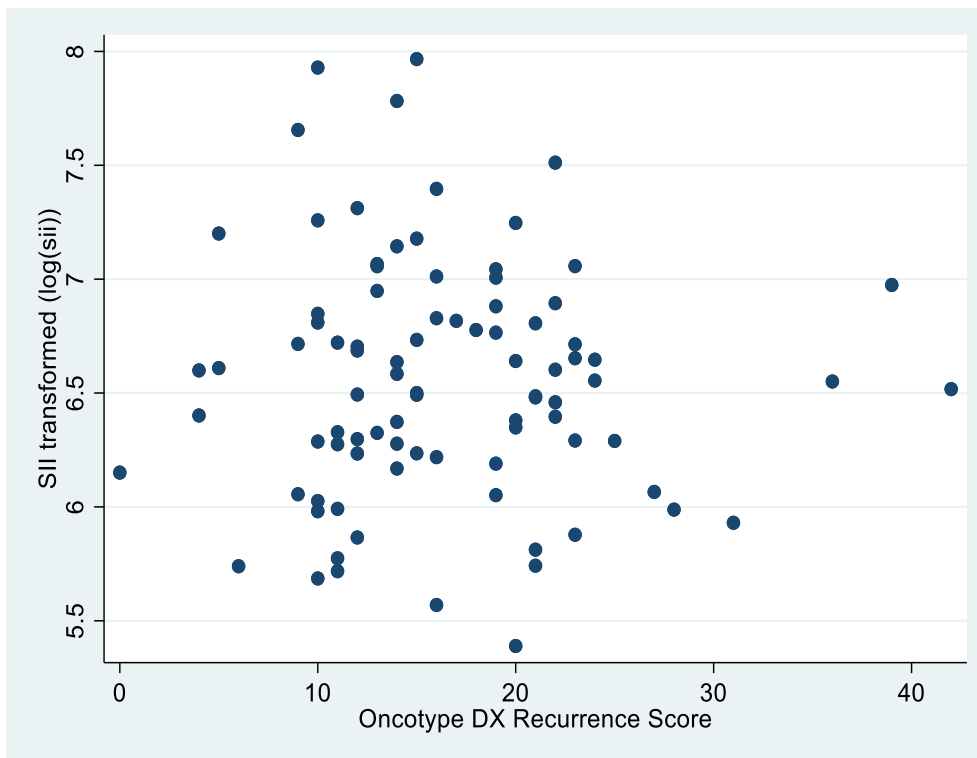


Figure 4.25 Correlation between Oncotype DX® RS and SII Lobular Cohort

Note: Spearman's rho correlation coefficient $rs(98)=[-0.031]$ $p<.001$

4.4.7.5 Oncotype DX® RS and NPI in Lobular Breast Cancer

The lobular cohort data was evaluated to explore whether there was any correlation of NPI and RS. Descriptive analysis confirmed that neither variable was normally distributed. Figure 4.26 suggests that in this cohort of patients with lobular breast cancer, there is no association between RS and NPI $rs(98)=[.123]$, $p=[.253]$ (Figure 4.26).

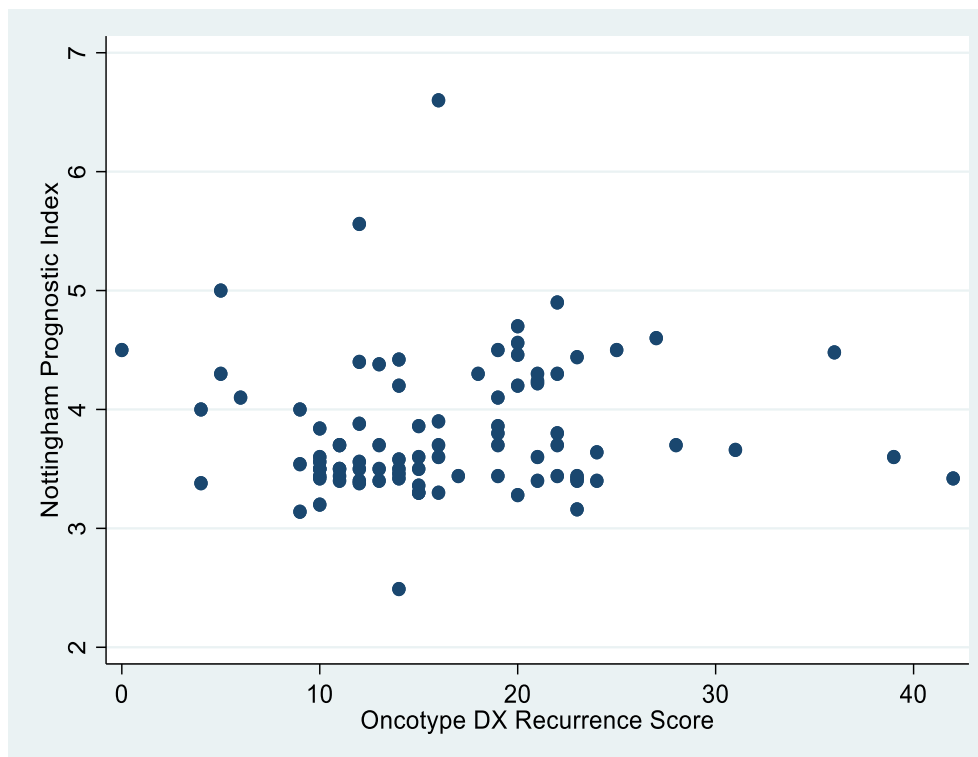


Figure 4.26 Correlation between Oncotype DX® and NPI in ILC

Note: Spearman's rho correlation coefficient $rs(98)=[.123]$, $p=[.253]$.

4.4.7.6 Lobular PR Negativity and Oncotype DX® RS

Oncotype DX® RS includes progesterone receptor expression in the formula for the recurrence score. As such, *PR* is associated with RS. In this cohort of lobular patients, nonparametric correlation suggests an association between *PR* negativity and RS. Fishers exact test $p=0.047$ (GRD).

The data of patients with *PR* negative ILC was analysed (n=16) (Table 4.7). The mean RS was 20.21, and median RS 18.5 (*SD* = 10.9). This is consistent with the literature, with most lobular cancers having a low to intermediate Oncotype DX® RS.

The mean and median NPI was 3.78 and 3.68 (*SD* = 0.399; Q1 3.48, Q2 3.68, Q4 4.08), respectively. This is consistent with the literature and illustrates the effect of Grade, with most lobular cancers being Grade 2.

The two pleomorphic ILC cases with *PR* negativity, both had high RS, although the NPI's were in the moderate risk group.

Table 4-7 ILC *PR* negative cohort

| Cohort No. | Age | NPI | ER/ <i>PR</i> | ODX RS | SII | Chemotherapy | Years since diagnosis |
|------------|-----|------|---------------|--------|------------|--------------|-----------------------|
| 99 | 59 | 3.5 | 8/2 | 13 | Normal | No | 12 |
| 103 | 58 | 4.3 | 8/0 | 18 | Normal | No | 10 |
| 114 | 65 | 3.86 | 7/2 | 19 | Raised NLR | Yes | 10 |
| 123† | 68 | 4.48 | 8/2 | 36 | Normal | Yes | 9 |
| 150 | 68 | 4.4 | 7/0 | 12 | Normal | No | 8 |
| 206 | 57 | 3.66 | 8/0 | 31 | Normal | Yes | 7 |
| 220† | 72 | 3.42 | 5/0 | 42 | Normal | Yes | 7 |
| 268 | 78 | 3.64 | 8/0 | 24 | Normal | No | 6 |
| 287 | 65 | 3.46 | 8/0 | 14 | Normal | No | 6 |
| 367 | 60 | 4.42 | 8/0 | 14 | Normal | No | 5 |
| 381 | 50 | 3.28 | 4/0 | 20 | Normal | Yes | 5 |
| 413 | 60 | 3.7 | 8/0 | 11 | Normal | No | 4 |
| 447 | 70 | 3.86 | 8/0 | 15 | Normal | No | 3 |
| 461 | 71 | 3.7 | 8/0 | 22 | Normal | No | 3 |
| 501 | 63 | 3.4 | 8/0 | 29 | Normal | Yes | 3 |
| 503 | 73 | 3.5 | 8/0 | 3.5 | Normal | No | 3 |

Note: †Pleomorphic grade 3 ILC. Patients in this cohort are all alive and well, with no evidence of recurrence.

4.5 DISCUSSION

4.5.1 Summary of the main findings

The study investigated the potential utility of systemic inflammatory indices as prognostic indicators in early ductal and lobular breast cancer. The ratios were calculated from the peripheral blood sample of a cohort of node negative patients from three district general hospitals in a single NHS Trust. Correlation between the Oncotype DX® recurrence scores with the indices was evaluated. The results suggest no association between the RS and any of the indices in the population studied. In addition, there was no clear association found between the RS and the NPI in the IDC or ILC patients in both age groups.

Over recent years, there has been considerable interest in the use of inflammatory indices as prognostic tools in solid cancers. Studies in breast cancer have assessed the use of the ratios in various subtypes, and at different stages of breast cancer, with varying results (Corbeau et al., 2020; Ethier et al., 2017). Similar studies to this one, evaluating the potential of the NLR in early breast cancer, have been published. Two retrospective reviews compared the Oncotype DX® RS and the NLR in early stage node negative breast cancer, with differing results (Alshamsan et al., 2021; Grenader et al, 2015). Grenader and colleagues (2015), in a study of 242 patients with Oncotype DX® RS testing, with no differentiation of subtype, found no association between the RS and NLR (Spearman's correlation $r_s=.852$). The study used a NLR cutoff level of 2.5. These results align with the Spearman's rho correlation coefficient in this study, which also confirmed no association with either subgroup (Ductal $r_s=.089$, Lobular $r_s=-.013$). However, the study by Alshamsan and colleagues (2021) suggested a correlation between the RS and NLR in their study of 160 patients. A 2.1 NLR cutoff was used. Multivariate analysis found that NLR and tumour grade were predictive of a high recurrence score. It is worth noting that, in the study lobular cancers comprised only 5.6% of the cohort (Alshamsan et al., 2021), a figure that is lower than the incidence of ILC (7-15%).

These two studies highlight the difficulties when evaluating the evidence for the use of systemic inflammatory indices as prognostic tools for breast cancer. The reference ranges used in studies vary, and the inclusion of different breast cancer subtypes may

influence results. These issues were noted in a systematic review and meta-analysis of publications investigating the association between NLR and breast cancer (Ethier et al., 2017). The cutoff levels for NLR ranged between 1.9 and 5.0, with a median level of 3. The decision to use a NLR of 3.5 in this study, in addition to the other ratio cutoffs referenced, was based on prospective population data evaluating normal levels of white cell based inflammatory markers (Fest et al., 2018; Forget et al., 2017). This approach was designed to reflect normal ratios in the adult population, providing context for discussion. The results from these population studies warrant further discussion. Both publications aimed to provide standardised reference levels for the NLR (Forget et al., 2017) and for other ratios from the peripheral blood test (Fest et al., 2018). The authors recognised that the reference ranges used in the literature for risk assessment varied widely. Inflammatory indices differ between males and females, and in addition, the levels increase with age (Fest et al., 2018). The reference ranges of the inflammatory indices in women over 45 years of age were used in this study (Fest et al., 2018).

The results of this study suggest that the use of the systemic inflammatory indices for prognostication in breast cancer may warrant further investigation. The use of the Glasgow Prognostic Score (CRP and albumin level), the NPI and NLR could be further explored in a defined population such as lobular breast patients.

4.5.2 Clinicopathological Features of the Tumour Groups

The population studied had clinicopathological features that were consistent with those in the published literature (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008). The mean patient age of the total cohort at diagnosis was 59 years (range 28 to 82). The mean age of this group of cohort was 62.76 years in the ductal tumour group and 63.84 in the lobular cohort (Table 4.1). This is consistent with the literature, as ILC is more common in the older age group (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008).

The lobular cohort were older and had larger tumour sizes than the patients with IDC. The mastectomy rates were also higher in the lobular cohort, especially in the under

50 age group, a probable consequence of the larger tumour sizes, in keeping with published literature (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008) (Table 4.2).

Large studies have found that most lobular tumours are Grade 2, with a small number of Grade 1 and 3 cancers (Arpino et al., 2004; Oesterreich et al., 2022; Pestalozzi et al., 2008). The histological tumour grade of the cohort was consistent with population studies, where most of the tumours in the cohort were Grade 2. The findings of this investigation confirm this, especially in the under 50 year age group, with no patients with Grade 1 tumours, and most cases having Grade 2 cancers (81.82%; n=9). The percentage of Grade 3 tumours in the lobular group (6%) is also consistent with the literature (Oesterreich et al., 2022; Pestalozzi et al., 2008). This may reflect the selection process for RS testing, with pleomorphic Grade 3 ILC's being considered for chemotherapy without genomic testing. Although, there were two pleomorphic cases included in the study, both of which had high RS, requiring chemotherapy. These two patients remain alive and well, 5 and 7 years post diagnosis. Indeed, there were few deaths in the cohort, limiting analysis. However, the results from this study align with the literature, with lobular cases typically presenting with late relapse.

4.5.3 Prognostic Assessment in ILC

Following surgery for hormone receptor positive early breast cancer, consideration is given to the use of adjuvant therapy. Treatments such as endocrine therapy and chemotherapy can reduce the risk of recurrence and improve survival. Clinicopathological factors used to assess the benefit of chemotherapy include the NPI, incorporating tumour size and grade, along with lymph node status. Although this provides some prognostic information, the need to consider the molecular tumour profile is evident, and the integration of the NPI with the results of genomic signatures has been shown to improve prognostication, and, in addition, triage the use of chemotherapy (Dowsett & Turner., 2019). The use of chemotherapy in this study is consistent with the literature which suggests that multigene panel testing reduces the number of patients requiring adjuvant chemotherapy by at least two thirds (Carlson &

Roth., 2013; Loncaster et al., 2017). As expected, more ductal than lobular patients received chemotherapy, 20% and 16%, respectively.

The results from this study highlight the importance of tumour grade. In the IDC cohort of patients under the age of 50, all the Grade 3 ductal cancers had high RS (n=13), although the small number of patients may have influenced the results. In the older age category, half of the Grade 3 tumours had a high RS. However, this study did not establish a clear association between grade and RS in the lobular cohort of patients. Most of the cases were Grade 1 or 2 (94%), with low to intermediate RS. The results of the NPI in this group of patients were also in the good to moderate risk categories, with the level being primarily dictated by tumour size. Although, there were six Grade 3 lobular cancers in the study, the NPI of all the cases was in the moderate risk group, with 50% of these having a high RS.

Histological grade is recognised as an important factor when considering breast cancer prognosis. With the implementation of breast screening, there has been a reduction in tumour sizes (Welch et al., 2016), and node positive disease at presentation (Hanrahan et al., 2006), such that the NPI calculation is often mostly based on tumour grade. However, pathological grading of tumours can be subject to interobserver variability in reporting, with discrepancies well documented in the literature (Robbins et al., 1996; van Dooijeweert et al., 2020). The emergence of AI in breast cancer pathology reporting may help address this (van Dooijeweert et al., 2022). Although this study did not find a strong association with tumour grade in the lobular cohort, published data suggests that grade is of prognostic significance especially in this breast cancer subtype (Engstrøm et al., 2015; Rakha et al., 2008).

There were 4 deaths in the ILC group of patients (Table 4.6). The RS ranged from 5 to 39. Three of the patients (75%) received adjuvant chemotherapy. All the patients were prescribed endocrine therapy. The patient with the RS of 5, did not receive chemotherapy and died within 2 years of diagnosis, with bone and brain metastases, aged 67. There were no significant comorbidities. The NPI was high, and the systemic inflammatory indices (SII, NLR and MLR) were also elevated. The hormone receptor status was *ER8*, *PR5*. This highlights how molecular profiling tests fail to identify every patient at high risk of relapse, findings which have been noted by other investigators (Abel et al., 2022; Felts et al., 2017). One of the deaths was in a 41 year

old patient with a RS of 21. She received adjuvant chemotherapy, and was on Tamoxifen when she presented with bone, liver and lung metastases two years after diagnosis. This is interesting as studies suggest that lobular cancers may demonstrate a greater resistance to Letrozole (Metzger-Filho et al., 2015).

One of the genes assessed in the Oncotype DX® RS testing is progesterone receptor status. This study reviewed the *PR* negative cases of ILC to evaluate the outcomes, NPI, RS and inflammatory indices in this group of patients. There were 16 patients with *PR* negative lobular cancer. All patients were in the over 50 age group. The median RS was 18.5 (Range 3.5 to 42), with 4 cases (25%) in the high RS group. The median NPI was 3.68, with no high NPI scores. In one patient, a 65 year old lady, the NPI was 3.86, *ER* 8, *PR* 2, RS 19, and the NLR was raised. She received adjuvant chemotherapy following a discussion with the oncologist. She is alive and well 10 years later. The results of the analysis of the *PR* negative lobular cohort differ somewhat with those published in 2008 by Orvieto et al. This retrospective analysis of 530 patients with ILC, which were analysed by lobular subtype, suggested that traditional clinicopathologic features such as Grade and *PR* status were strong predictors of outcome, followed by age, tumour size, and the presence of lymphovascular invasion. The smaller sample size in this study may have failed to identify the significance of *PR* status, and, in addition, the lobular cohort were preselected for RS testing, which may be a confounding factor. However, Oesterreich and colleagues (2022), also noted in their investigation which assessed the clinicopathological outcomes of 3617 patients with ILC, that a negative *PR* did not confer poor prognosis.

The findings of this study suggest that prognostication in the lobular breast cancer subtype may require a different approach. Researchers are investigating the use of specific markers that may improve the identification of lobular cancers. The use of H&E staining, assessment of E-Cadherin expression, in conjunction with DNA mutation of *CDHI* has been shown to improve the diagnostic accuracy for lobular cancers (Ciriello et al., 2015).

4.5.4 Limitations

This study has several limitations. It is retrospective study from a single NHS UHB which may have resulted in confounding and selection bias. The unit, like most breast units in the UK, request RS testing on tumours with pathology sizes greater than 19mm. Therefore, this cohort may not represent results in other countries, where testing may be performed with different thresholds.

Additionally, the outcome data may not reflect those in the literature, as there was a low rate of recurrence and mortality in this cohort of patients, such that a type II statistical error may have occurred in the analysis. Inclusion of node positive disease may have enhanced the analysis, and this may be considered in future work, especially as results from the RxPONDER (Kalinsky et al., 2021) and MINDACT trials (Piccart et al., 2021), suggest that some patients with low nodal positivity may be spared adjuvant chemotherapy.

An additional point to note, is that the population investigated is ethnically homogeneous, and maybe less diverse than many of the published studies, with the ethnicity of the study group being Caucasian. The study should be repeated on a larger diverse population to get estimates for different ethnicities. However, it could be argued that there may be less variability in the systemic inflammatory indices reference levels, as it is recognised that the ratios differ with ethnicity (Farmer et al., 2022).

4.6 CONCLUSION

In summary, this study found no correlation between the Oncotype DX® RS and the Systemic Inflammatory Indices evaluated. In addition, subanalysis of the lobular cohort of patients confirmed that there was also no association between the NPI and the Oncotype DX® RS. Literature suggests that raised NLR and SII are poor prognostic signs. However, this was not evident in this sample of patients.

CHAPTER 5: FINAL DISCUSSION AND CONCLUSION

5.1 INTRODUCTION

The work presented in this thesis evaluates the preoperative assessment and prognostication of lobular breast cancer. The growth pattern and the distinct histomolecular nature of this subtype can present difficulties with diagnosis, management, and prognostication. The thesis investigated the correlation of lobular tumour size assessed on tomosynthesis and, in addition, the use of systemic inflammatory indices as prognostic tools in early breast cancer. Both interventions studied are readily available, quick to perform, and are part of the routine workup of breast patients.

5.2 PREOPERATIVE IMAGING ASSESSMENT

Most patients diagnosed with early breast cancer will have been evaluated with standard breast imaging in the form of sonography, and mammography, both usually performed prior to biopsy. Following the histological confirmation of a lobular neoplasm the management is discussed at a breast MDT, if the lesion is suitable for conservative surgery, and the patient wishes to avoid mastectomy, a breast MRI is requested. The time to surgery can be delayed waiting for the imaging to be arranged, reported, and then to be rediscussed. As previously stated (Chapter 1), there are several situations which preclude MRI imaging. There are patient factors, such as claustrophobia, metallic implants, reactions to the contrast agent, and body mass index, which can be contraindications to the procedure. Additionally, there can be a delay in the time to surgery waiting for the investigation, and after, if further assessment and biopsies are required (Bleicher et al., 2009; Chandwani et al., 2014). This study assessed the use of digital breast tomosynthesis in the preoperative assessment of invasive lobular cancer. The work investigated whether the introduction of this technology had improved lesion measurement such that the need for breast MRI may be reduced.

The size of the index lesion was measured with both imaging modalities (MRI and DBT) and compared with the final pathology size to evaluate concordance. Overall, the results from this study reaffirms clinical practice, in that preoperative ILC size assessment is best assessed with MRI, with Spearman's correlation for DBT $r(94)=[.487]$, $p<.001$, and MRI $r(94)=[.608]$, $p<.001$. This study demonstrated similar correlations for tomosynthesis as those described in the literature (Chamming's et al., 2017; Garlashi et al., 2019; Girometti et al., 2018). Some of the stronger correlations published were seen in studies with mixed tumour groups, analysing a small number of ILC cases within that dataset (Förnvik et al., 2010; Förnvik et al., 2018; Seo et al., 2013; Wall et al., 2011). Although ILC is the most common special type of breast cancer, the incidence is relatively low, accounting for 7-15%. Therefore, to obtain a large sample size for analysis, multicentre studies would be needed, even in large units. Prospective studies in screening can recruit greater patient numbers, although the lobular cohort is often analysed as a subanalysis (Van Baelen et al., 2022), which can confound results (Brookes et al., 2001). Additionally, it is worth noting that many of the study cohorts in screening settings detect smaller tumours than those presenting in symptomatic clinics, which may also be a confounding factor in some of the published studies (Welch et al., 2016). Results in the literature suggest a higher ILC detection rate with DBT, with limited evidence regarding an improvement in tumour size evaluation for this subtype, as demonstrated in this study.

Breast density has been the topic of discussion on both sides of the Atlantic, with the USA incorporating density into screening guidelines (Melnikow et al., 2016). The UK has been considering modifying mammographic screening frequency for individuals based on breast density, with a move toward less frequent imaging for patients with fatty breast tissue (McWilliams et al., 2022). A recent literature review (Clift et al., 2022), investigating the evidence for a stratified approach to breast screening, concluded that currently there was insufficient evidence to support a change in practice. This study evaluated size correlation for the two density groups to investigate whether measurement was more accurate in less dense breast tissue. The results confirmed an improvement in size assessment in less dense breast tissue, with correlation coefficients for density category 1 (A+B) $r_s(64)=[.560]$, $p<.001$, and $r_s(28)=[.371]$, $p=[.044]$ for patients with dense breasts (Category C+D). However, it is worth noting that the sample number was low for the dense breast group. Although,

consistent with the literature (Chudgar et al., 2017; Conant et al., 2019; Rafferty et al., 2016), these results remain lower than the MRI correlation in this group ($r_s=[.608]$; $p<.001$).

Lesion measurement can be challenging, especially with large tumour sizes in dense breast tissue (Marinovich et al., 2018; Vijayaraghavan et al., 2018). The study investigated tomosynthesis measurement of ILC by DBT for each tumour group size (T1 and T2). The results of this study align with the literature (Gest et al., 2020), with tomosynthesis demonstrating moderate to good correlation with pathology in the size assessment of the smaller tumours (T1), and increasing discordance with larger tumours, especially in the presence of extensive in-situ components and calcification (Marinovich et al., 2018; Vijayaraghavan et al., 2018). These latter imaging findings contributed to the outliers in this dataset. These large discrepancies between DBT and pathology size resulted in a significant underestimation of disease extent. However, it can be argued that the correlation with MRI was also insufficient in these cases, as the technology resulted in overestimation of lesion size in some of these cases, increasing the mastectomy rate, an effect that is well documented in the literature (Houssami et al., 2008; Mann, 2010; Parvaiz et al., 2016).

It is important to consider clinical practice when reviewing the results of a study. During surgery, tumour margins are considered clear if there is no tumour at the edge of the specimen (Moran et al., 2014), with margins in the UK considered clear at 1mm (Bundred et al., 2022). HDUHB surgical teams radiologically assess macroscopic tumour margins before closing the wound. Although, this is not a fail-safe way of excluding margin involvement, gross pathology can usually be seen on the image which can guide excision. This study analysed the data with a tolerance of 5mm, in an attempt to mirror surgical practice. The results show that when this tolerance is added to the evaluation, the size of 67.5% of T1 lesions, and 37.5% of T2+T3 tumours assessed on tomosynthesis were concordant with final pathology measurement. This difference was more obvious when the tolerance was added to the two breast density groups, with underestimation of tumour size in 28.8% of the low density group compared with 53.3% of the dense group. These findings highlight the negative effect of breast density when measuring lobular tumours.

Advances in breast imaging technology have led to the widespread use of tomosynthesis in screening and symptomatic settings in the UK, as studies have demonstrated higher cancer detection rates when compared with standard digital mammography. This improvement is mostly due to improved margin delineation, a reduction in anatomical noise and tissue overlay (Chamming's et al., 2017; Destounis et al., 2013, Girometti et al., 2018; Mariscotti et al., 2016; Michell & Batochi., 2018). Despite this refinement, the technology has not resulted in a significant improvement in lesion assessment of ILC, such that MR imaging is not needed. Recent studies investigating the use of contrast-enhanced digital mammography have shown promising results, independent of breast density, suggesting that this CESM/CEDM may be a viable alternative to breast MRI (Daniaux et al., 2023; Fallenberg et al., 2016; Lee-Falker et al., 2017; Lobbes et al., 2015). However, further work is needed to evaluate the technology in patients with ILC, as studies have suggested that CESM can also overestimate tumour size, potentially increasing mastectomy rates (Sumkin et al., 2019).

5.3 SYSTEMIC INFLAMMATORY INDICES IN LOBULAR BREAST CANCER

Following definitive surgery for hormone receptor positive early breast cancer, decisions surrounding adjuvant therapy for patients with lobular tumours can be challenging. Results from studies assessing treatments and prognostication are based on a cohort of different subtypes, and often biased toward ductal cancer responses, extrapolating the findings to apply to the lobular cohort. However, it is well recognised in the research community that these special subtypes may need an individualised approach that incorporates the unique molecular and morphological features of ILC. Prognostication in early breast cancer in the adjuvant setting has been evolving from this “one size fits all” approach to a more personalised assessment of clinical, histological, and molecular characteristics of the tumour. The NPI remains a useful bedside tool, and the development of the Nottingham Prognostic Index Plus (NPI+) decision making tool, which incorporates additional factors such as the number of positive nodes, lymphovascular invasion, *ER*, *PR* and *HER2* status, has shown promise (Green et al., 2016). This has been integrated into the American Joint Committee on

Cancer Breast Cancer Staging System (Chavez-MacGregor et al., 2017). However, the results are dependent on accurate and standardised pathological reporting of tumour type, grade, and size, along with identification of lymphovascular invasion. This can be problematic in practice, especially in the histological assessment of lobular breast cancer (De Schepper et al., 2022; Khazai et al., 2015).

This study evaluated the use of the systemic inflammatory indices calculated from the preoperative peripheral blood analysis in patients with node negative, early breast cancer who had received Oncotype DX® RS testing. The hypothesis investigated was that a correlation between the RS and the inflammatory indices may exist such that the indices could provide reliable prognostication in patients with ILC. Published studies evaluating the prognostic value of systemic inflammatory indices in solid tumours, suggest that the ratios may have potential as prognostic markers (Faria et al., 2016; Paramanathan et al., 2014; Yang et al., 2018). These indices are easily obtained and as they are performed as part of the preoperative workup in most breast patients, they are cost neutral. However, standardisation of thresholds in the literature is not consistent, so extrapolation of findings is problematic. This study referred to reference levels obtained from prospective studies to provide standard thresholds for the inflammatory indices (Fest et al., 2018; Forget et al., 2017).

The thesis presented the Oncotype DX® RS, NPI and systemic inflammatory indices results of 395 IDC and 100 ILC, in node negative patients. Spearman's rho correlation testing confirmed a weak correlation between the NLR and the RS in the ductal group ($r(394)=[.126]$, [$p=.007$]) and with very weak correlation in the ILC group ($r(98)=[-.126]$; [$p=.105$]). Interestingly, although there was very weak correlation between the RS and the NPI in the lobular cohort ($r(98)=[.060]$; [$p=.278$]), there was weak correlation between the NPI and RS in the ductal group of patients ($r(394)=.343$; $p=.001$). These results highlight the issues with prognostication in lobular patients. The tumours are often Grade 2, so the NPI is mainly dependent on size and nodal status in ILC. This group of patients were node negative, thereby reducing the NPI to tumour size. Other inflammatory markers may prove better indicators in lobular cancers, such as The Glasgow Prognostic Score and modified Score, which combine the CRP and Albumin level. Although published studies have demonstrated some correlation with

survival in early breast cancer, further work would be needed to use the results to stratify outcome, especially in specific subtypes (McMillan., 2013).

The concept of personalised medicine has become forefront in many medical disciplines with the aim of tailoring treatment to individual patients. The field of breast surgical oncology has embraced this, moving from traditional risk assessment tools such as the Nottingham Prognostic Index (NPI), to clinically validated gene-expression tests to predict recurrence and to guide chemotherapy decisions in early breast cancer. This shift from pathological factors such as lymph node status, tumour size and grade to molecular signaling pathways and genetic signatures occurred in the pursuit of representing the true heterogeneity of breast cancer more accurately. However, studies have shown that lobular cancers are a unique type of breast neoplasm that is often underrepresented in trials, such that evidence of benefit is extrapolated from data collated from studies on other subtypes. This limiting factor is highlighted in the discrepant risk stratification results that can result when applying different molecular prognostic tests to the same tumour. One study comparing the results of MammaPrint and Oncotype DX® RS, found recurrence score concordance in only 77% of a dataset of 295 samples (Fan et al., 2006).

Prospective trials designed for a lobular cohort may provide the evidence for personalised treatment options for this cohort of breast cancer patient. Current research into genomic profiling has seen the development of a test specifically designed for ILC (McCart-Reed et al., 2019). Lobsig is a multigene test which is under validation for prognostication in lobular cancers (McCart Reed et al., 2019). Indeed, advances in genomic profiling have opened opportunities that can be explored for this subgroup. A recent study analysing circulating DNA in lobular patients noted a higher proportion of specific mutations that could be potential targets for treatment options (Davis et al., 2022).

It is now accepted that ILC represents a distinct subset of breast cancer, which is defined by loss or genetic aberrations in the E-cadherin gene, with high percentage of *ER* positive disease and low *HER2* positive disease (McCart Reed et al., 2015). These features partly explain the presentation, imaging findings, response to treatment, and outcomes of lobular cancers. Following the publication by Foote and Stewart in 1946 describing the growth pattern of ILC, research is still uncovering unique hallmark

features that may improve identification of lobular subtypes, facilitate the development of lobular specific prognostic systems and therapeutic agents, with the aim of improving outcomes for patients.

5.4 LIMITATIONS

The two studies presented in this thesis have several limitations in addition to the retrospective design, as outlined in Chapters 3 and 4. Although trial recruitment continued until 2020, and the cohort size was larger than many of the published studies in the symptomatic setting, sample size was a factor in the imaging study. Missing images with all modalities resulted in a reduction in the size of the cohort. The study period included the time through the COVID-19 pandemic. Two factors reduced the number of cases that fulfilled the study design. Firstly, a significant number of patients received adjuvant endocrine therapy which excluded inclusion into the trial. Also, it was evident that patient reluctance to travel for preoperative MRI, coupled with the concern that further surgery may be needed, may have influenced the number undergoing mastectomy, resulting in potential selection bias. Additionally, the mastectomy rate of the patient population in Southwest Wales maybe higher than other regions in the UK, which may also be a limiting factor when comparing outcomes in different populations.

Interobserver variation in image analysis is well recognised in the literature. The two readers interpreting DBT have worked together over two decades. Other studies have employed more than two readers, and this was considered. However, time, workload and financial constraints precluded this.

In both studies, the cohort investigated was racially and ethnically homogenous, and less diverse than in some of the published research. Although there may be some advantages in studying these cases as this reduces the risk of ethnic variability, the findings may not be transferable to different populations. This limitation could be addressed in a multicentre study, as it is important to include racial diversity in trials to ensure health equality.

5.5 FUTURE STUDIES

The studies described in this thesis highlight the potential for further research. The mastectomy rate in the more remote catchment areas of HDUHB could be addressed to explore whether there are factors that may improve patient choice and decision making. The use of digital technology by keyworkers to support newly diagnosed patients in the preoperative setting would be an exciting innovation to investigate. This could potentially facilitate preoperative discussions to improve informed consent, which may positively influence surgical choice in Southwest Wales.

The development of CESM, and the introduction of the technology in HDUHB, opens the possibility of a prospective multicentre multireader study comparing CESM, MRI and DBT for imaging newly diagnosed patients with ILC. The research presented in the first part of this thesis could be repeated as a prospective study with the addition of CESM to MRI, with the potential to address some of the limitations highlighted above. In addition, the unit will have the opportunity to incorporate CAD into the trial design.

Prognostication in breast cancer is an important part of a patient's journey. The adage 'one size fits all' does not apply to breast cancer. Development and evolution of molecular profiling has highlighted the need for more targeted testing. Following on from the research on SII's, exploring the prognostic ability of SII with the markers used in the GPS (creatinine and CRP), and the NPI could be considered in a future study. This could evolve into the development of a nomogram incorporating the scores of the indices to investigate whether this identifies cases where genomic testing could potentially be omitted. In addition, with the increased use of AI in pathology, it may be possible for laboratories in the UK to standardise *Ki-67* assessment cost effectively. A further study could evaluate the use of the nomogram incorporating *Ki-67* to explore whether this may have potential as a prognostic indicator in early breast cancer. As approximately a third of patients undergoing multigene panel testing in early breast cancer are in the lower risk group, thereby avoiding chemotherapy, identifying these individuals prior to testing would result in significant savings to the health service.

5.6 CONCLUSION

Survival rates from breast cancer continue to improve. The detection of smaller tumours at an earlier stage, coupled with therapeutic advances, have all contributed to the reduction in mortality rates in developed nations. Although the diagnosis and management of breast cancer has evolved, the nature of invasive lobular breast cancer can present specific challenges. The imaging findings and response to treatments of this subtype are such that a unique approach to lobular cancer has been suggested by scientists working in this field.

Although mammography remains an essential tool in both the screening and symptomatic settings, there are well recognised limitations when imaging lobular neoplasms. Despite the technological advancements in the digital platform, which have facilitated development in breast imaging to progress from standard digital mammography to breast tomosynthesis, with the latter demonstrating a higher cancer detection rate than digital mammography, missed cancer rates are still significant especially in the lobular cohort (Korhonen et al., 2016). In addition, the inference that enhanced margin assessment with tomosynthesis may translate to improved preoperative size assessment for lobular cancer, has yet to result in a reduced need for breast MR imaging.

This study failed to demonstrate a sufficient level of agreement between size on histology and tomosynthesis tumour measurement in the preoperative assessment of ILC that would reduce the need for breast MRI in patients planned for conservative surgery. The introduction of computerised analysis and contrast-enhanced digital imaging may address some of these shortfalls, as evidence is growing on the advantages of this emerging technology for breast cancer staging. The sensitivity and specificity for detection of breast cancer and size assessment with both tomosynthesis and CESM imaging modalities will improve with the move toward integration of AI. Research into radiomics is proceeding at pace. This latest technique is being investigated, as the ability to apply computational algorithms to extract information from an image to provide quantitative details is promising. Although in their infancy, these applications may prove beneficial in aspects of breast evaluation that continue to present diagnostic difficulties such as those posed by ILC.

The complexities surrounding lobular cancers also extend to prognostication. The pattern of metastatic spread, often years after diagnosis, and to less common anatomical sites than other breast tumours, continue to challenge the breast community. The inherent difficulties with histological confirmation of ILC and the identification of lobular subtypes, has attracted scientists and survivor groups to lobby the research community to conduct specific studies on this subtype. Groups, such as The Lobular Breast Cancer Care Alliance (LBCCA), are funding scientists to facilitate pioneering research investigating new approaches to ILC, with the aim of improving outcomes. Recent work by the scientific team at LBCCA developed a lobular specific experimental model which has been used to identify potential targets for new therapeutic agents (Sflomos et al., 2021). The group have also highlighted the importance of accurate identification of ILC after conducting a study involving 35 pathologists from nine countries which found significant interobserver variability (Christgen et al., 2022). Further global collaboration with histopathologists has been undertaken to produce a universally agreed set of criteria (De Schepper et al., 2022). Improved diagnostic criteria for ILC is a prerequisite for lobular specific studies, as extrapolating findings from research conducted on all breast tumour subtypes may not benefit patients with lobular cancer. The use of AI in pathology has the potential to improve diagnostic reliability for ILC.

In Chapter 4 of this thesis, the use of systemic inflammatory indices obtained from preoperative peripheral blood parameters was investigated to assess a potential association with Oncotype DX® RS. This study found no correlation in this cohort of patients, analysing each subgroup separately, or with the lobular cancer group that was investigated separately.

An editorial in the NEJM published in 2016 summarises the issues surrounding the concept of personalised medicine (Hunter, D.J., 2016). The advent of new methods of prognostication may not translate to greater certainty, rather this may increase uncertainty. Even in this era of AI, this premise may still hold true. Although challenges remain, the quest to improve patient outcomes drives the research community to identify new markers to develop tools and treatments. Efforts which are welcomed by both clinicians and patients.

APPENDIX

APPENDIX 1: DATA COLLECTION FORM A - MAMMOGRAPHY

| | |
|---------------------------|--|
| READER NUMBER | |
| PATIENT ID | |
| DBT MEASUREMENT | |
| SLAB NUMBER | |
| C-VIEW MEASUREMENT | |



PRIMARY LESION

(Please mark all lesions on diagram)

| DESCRIPTOR | DBT | s2D/C-VIEW |
|-------------------------|-----|------------|
| SIZE | | |
| SITE | | |
| ABNORMALITY | | |
| DENSITY CATEGORY | | |

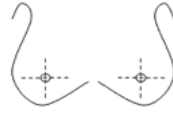
ADDITIONAL FINDINGS

| | DBT | s2D/C-VIEW |
|--------------------|-----|------------|
| SIZE | | |
| SITE | | |
| ABNORMALITY | | |

| MAMMOGRAPHIC ABNORMALITY |
|-------------------------------|
| N = NONE/NORMAL |
| SM = SPICULATED MASS |
| M = WELL DEFINED MASS |
| AD = ARCHITECTURAL DISTORTION |
| MC = MICROCALCIFICATION |
| AS = ASYMMETRY |

APPENDIX 2: DATA COLLECTION FORM B - MRI

Patient Identification Number:



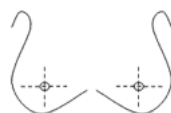
PRIMARY LESION

(Please mark all lesions on diagram above):

| MRI FINDINGS | |
|----------------------------|--|
| SIZE | |
| SITE | |
| ABNORMALITY | |
| ADDITIONAL FINDINGS | |
| SIZE | |
| SITE | |
| ABNORMALITY | |

APPENDIX 3: DATA COLLECTION FORM C - SONOGRAPHY

| | |
|------------------------|--|
| PATIENT ID | |
| READER NUMBER | |
| DATE OF IMAGING | |



PRIMARY LESION

(Please mark all lesions on diagram)

| DESCRIPTOR | SONOGRAPHIC FINDINGS |
|----------------------------|-----------------------------|
| SIZE | |
| SITE | |
| ABNORMALITY | |
| ADDITIONAL FINDINGS | |
| SIZE | |
| SITE | |
| ABNORMALITY | |

APPENDIX 4: DATA COLLECTION FORM D: PATHOLOGY

Patient Identification Number:

| PATHOLOGY FINDINGS | | | |
|------------------------------------------|------|------|------|
| AGE | | | |
| YEAR OF DIAGNOSIS | | | |
| OPERATION DETAILS | | | |
| REOPERATION YES/NO – DETAILS | | | |
| INVASIVE HISTOLOGY | | | |
| GRADE ILC | | | |
| INVASIVE TUMOUR SIZE (PRIMARY LESION mm) | | | |
| ADDITIONAL INVASIVE FOCI ILC | | | |
| LYMPH NODE STATUS | | | |
| HORMONE/NEU- RECEPTOR STATUS: | ER | PR | HER2 |
| INTRADUCTAL COMPONENT | | | |
| INTRADUCTAL COMPONENT (YES/NO) | | | |
| HISTOLOGY DCIS/LCIS | | | |
| SIZE INTRADUCTAL COMPONENT (mm) | DCIS | LCIS | |
| ADDITIONAL FINDINGS | | | |
| SIZE | | | |
| SITE | | | |
| ABNORMALITY | | | |

APPENDIX 5: STATISTICAL ANALYSIS SII

The two accepted measures of non-parametric rank correlation are Kendall's tau and Spearman's (rho) rank correlation coefficient. These analyses were used to measure the strength of the relationship between the variables. Kendall's Tau: usually smaller values than Spearman's rho correlation. Calculations are based on concordant and discordant pairs. This test is insensitive to error. *P* values are more accurate with smaller sample sizes. Spearman's rho: usually have larger values than Kendall's Tau. The calculations are based in deviations. These are more sensitive to error and discrepancies in data. Professor Paul. D. Lewis assisted with the analysis.

| | Kendall's Tau B | | Spearman's Rho | |
|---------------------------|-------------------------|----------------------------------|-------------------------|----------------------------------|
| | Correlation Coefficient | Significance <i>p</i> (2-tailed) | Correlation Coefficient | Significance <i>p</i> (2-tailed) |
| Ductal Cohort | | | | |
| IDC RS v NLR (All cases) | .057 | .137 | .089 | .116 |
| IDC: RS v NLR >=50 | .059 | .177 | .092 | .152 |
| IDC: RS v NLR <50 | .030 | .715 | .046 | .708 |
| RS>25: IDC RS v NLR | -.058 | .483 | -.072 | .551 |
| RS<=25: IDC RS v NLR | -.042 | .339 | -.056 | .382 |
| NLR>3.53: IDC v NLR | .079 | .358 | .109 | .389 |
| NLR<=3.53: IDC v NLR | -.002 | .972 | .002 | .970 |
| IDC: RS v SII (All cases) | .048 | .213 | .069 | .221 |
| IDC: RS v SII >=50 | .033 | .453 | .045 | .480 |
| IDC: RS v SII <50 | .096 | .247 | .142 | .241 |
| IDC: RS>25 RS v SII | .096 | .247 | .142 | .241 |
| IDC: RS<=25 RS v SII | -.047 | .289 | -.070 | .277 |
| IDC: NLR>3.53 RS v SII | .083 | .335 | .103 | .415 |
| IDC: NLR<=3.53 RS v SII | -.020 | .645 | -.029 | .645 |

| | Kendall's Tau B | | Spearman's Rho | |
|----------------------|-------------------------|----------------------------------|-------------------------|----------------------------------|
| | Correlation Coefficient | Significance <i>p</i> (2-tailed) | Correlation Coefficient | Significance <i>p</i> (2-tailed) |
| Lobular Cohort | | | | |
| RS v NLR (All cases) | -.010 | .896 | -.013 | .907 |
| RS v NLR >=50 | .022 | .780 | .034 | .773 |
| RS v NLR <50 | -.230 | .365 | -.306 | .390 |
| RS>25: RS v NLR | .500 | .083 | .643 | .086 |
| RS<=25: RS v NLR | .063 | .426 | .097 | .400 |
| NLR>3.53: RS v NLR | -.190 | .213 | -.241 | .269 |
| NLR<=3.53: RS v NLR | .023 | .798 | .038 | .728 |
| RS v SII (All cases) | .028 | .709 | .069 | .221 |
| RS v SII >=50 | .066 | .411 | .096 | .411 |
| RS v SII <50 | -.230 | .365 | -.318 | .370 |
| RS>25 RS v SII | -.230 | .365 | -.318 | .370 |
| RS<=25 RSv SII | .101 | .200 | .141 | .217 |
| NLR>3.53 RS v SII | -.209 | .168 | -.292 | .177 |
| NLR<=3.53 RS v SII | .074 | .402 | .112 | .383 |

GLOSSARY

| | |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acini | Secretory units in the breast found at the end of each ductal system. |
| Acoustic Enhancement | Increased echoes deep to the lesion in the ultrasound field. |
| Acoustic Shadowing | A loss of signal appearing under a lesion. |
| Adjuvant Treatment | Therapy given after the main treatment employed to reduce the risk of cancer recurrence. |
| Allred Score | Scoring system used in oestrogen and progesterone receptor testing. |
| Anatomical Noise (Structural Noise) | The effect that normal anatomy can create in a radiological image. |
| Asymmetry | An area of increased density seen on mammography when compared with a corresponding area in the other breast. |
| Breast Cancer Index | Combines two independent biomarkers (HOXB13:IL17BR ratio (H/I)) and the molecular grade index that assess oestrogen mediated signalling and grade respectively. |
| Breast Conserving Surgery | Also known as lumpectomy. The abnormal area is removed, normally with a small amount of surrounding breast tissue. |
| Complex Sclerosing Lesion | Also known as a Radial Scar which is an imaging finding on mammography. |
| Contrast-Resolution | Ability to distinguish between differences in intensity in an image. |

| | |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C-View/Synthetic 2D | 2D reconstructed images from tomosynthesis data. No radiation required in production. |
| Desmoplastic Reaction | A tissue response to cancer, injury or inflammation. |
| Disease Free Survival | The time period that the patient is disease free after treatment for cancer. |
| Distortion | Term referring to focal disruption of the normal breast tissue seen on breast imaging. |
| E-cadherin | A transmembranal protein encoded by the <i>CDH1</i> gene. |
| EndoPredict® | Multigene assay assessing a panel of 8 cancer related genes (<i>UBE2C, DHCR7, BIRC5, RBBP8, IL6ST, AZGP1, MGP, STC2</i>), 3 normalisation genes (<i>CALM2, OAZ1, RPL37A</i>) and 1 control gene. |
| EPclin Risk Score | A prognostic parameter score of the risk of distant recurrence with 5 years of endocrine therapy. |
| Fat Necrosis | Loss of fat tissue due to injury due to injury and loss of blood supply. |
| Genomic Grade Index | Based on the expression of 97 genes. |
| Glasgow Prognostic System (GPS) | Scoring prognostic system based on serum C-reactive protein and albumin. |
| Haematoxylin & Eosin Staining | H&E is histological staining of tissues to aid diagnosis and margin assessment. |
| Isodense | Density of the lesion which is similar to the surrounding tissue. |

| | |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kinetic Enhancement | Breast enhancement curves seen in MRI. |
| Metastatic/Metastasis | Cancer spread from a primary site. |
| National Cancer Database | A USA clinical oncology database collated from hospital registry data from over 1500 accredited cancer hospitals. |
| Neoadjuvant | Treatment given before definitive surgery, usually refers to chemotherapy or endocrine therapy. |
| Occult | In respect of breast cancer, this is when the malignancy is not detected by routine imaging. |
| Oncoplastic Surgery | Surgical approach that aims to improve cosmesis. |
| Oncotype DX RS 21 gene assay | A quantitative reverse transcriptase polymerase chain reaction assay used for prediction of chemotherapy response and for prognostication in hormone receptor positive breast cancer. |
| MammoPrint assay | Microarray based test analysing the expression of 70 genes assessing recurrence risk in early breast cancer. |
| Prosigna Breast cancer Assay | A microarray based 50 gene assay test providing a risk of recurrence (ROR). |
| Population, Intervention, Comparison, Outcome | Statistical question formulated at the start of research to achieve aims and objectives. |
| Quantra Software | Computer breast density analysis system used in Hologic Selenia Tomosynthesis. |

| | |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Radial Scar | Also known as a Complex Sclerosing lesion which can be associated with breast cancer. |
| Radio-opaque | Refers to a dense area which appear white on mammography. |
| Sentinel Node Biopsy | Procedure to assess whether the tumour has spread to the draining lymph node. |
| Structural Noise | See Anatomical Noise |
| Summation Shadow | Refers to an area on a mammogram that is due to overlay of normal breast tissue which can flatten out with compression and repositioning. Summation is reduced by tomosynthesis. |
| Surveillance, Epidemiology, & End-Results Data | A validated source of cancer information and statistics in the USA collected from 1973. |
| Spicule/Spiculae (Plural) | Line/lines seen on an image of the breast, radiating from a tumour and caused by fibrosis. |
| Tomosynthesis Slice/Frame | DBT produces multi low dose images known as Slices/Frames, which are reconstructed for image interpretation. |
| Triple Assessment | Clinical, imaging and biopsy assessment of a breast lesion performed to reduce imaging pathology discordance. |
| Vacuum Assisted Biopsy | A biopsy performed under image guidance using vacuum to extract tissue for assessment and therapy. |

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